ENVIRONMENTAL RESEARCH 5, 1–58 (1972)

Mortality From Heat Illness and Heat-Aggravated Illness in the United States

F. P. ELLIS*

John B. Pierce Foundation Laboratory, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06519

Received August 21, 1971

INTRODUCTION

The "Indian Summer" weather towards the end of September 1970 caused an unexpected increase in the use of air-conditioning systems which overloaded the electrical power supplies of New York and other cities on the eastern seaboard of the United States. The air-cooling and dehumidifying systems of many apartment and office blocks were inactivated at the very time when optimum control of the thermal environment was most needed to ensure the comfort, working efficiency and health of the occupants. The maximum afternoon dry-bulb and wet-bulb temperatures at the New York Meteorological Observatory in Central Park were 91/75, 92/75, 83/73, 87/75, 90/73°F (32.8/23.9, 33.3/23.9, 28.3/22.8, 30.6/23.9, 32.2/22.8°) between the 22nd and the 26th of the month. The associated minimum temperatures at night were 72°F (22.2°), 77°F (25°), 75°F (23.9°), 72°F (22.2°) and 74°F (23.3°), although temperatures in the more congested areas and in buildings which were not air-conditioned would have been higher. This was a brief and not very severe heat wave occurring at a time of year when most people would still have been partially acclimatized after the summer (NOAA, 1970A).

On the first 3 days 256, 260 and 276 deaths from all causes were reported by date of occurrence to the New York City Health Department (Nelson, 1970). The average number of deaths for these 3 days was 264 and the standard error of this average, based on the assumption of a Poisson distribution, is 9.4. The 95% confidence limits for the mean are thus 245–283. When the figures for the remaining 27 days of the month are scrutinized the numbers of deaths reported on any one day only exceeded 245 on 2 occasions and one of these days was the 4th day of the heat wave. The greatest number of deaths occurred on the 3rd day when the temperature was less than on the previous 2 days. This is consistent with the observations of Kutschenreuter (1959) and, more recently, of Oechsli and Buechley (1970), that during heat waves the maximum number of heat deaths tends to follow the maximum temperature with a one-day lag. The evidence indicated that the number of deaths increased even during this small heat wave. Further evidence that the daily mortality had increased appreciably above the normal levels for that time of year was that during the subsequent 4-month period the high figure of 276 deaths on the 24th of September, normally

* Present address: 27 Bellsize Court, Wedderburn Rd., Hampstead, London NW3.

one of the healthiest months of the year, was only exceeded on 2 very cold days, the 28th and 29th of December, when there were 279 and 277 deaths respectively (Nelson, 1971).

Air pollution levels were also unhealthily high during the heat wave in sharp contrast with most other days in this month. However, with the exception of the well-documented British disaster of 1952 (Logan, 1953; Scott, 1953), which was associated with cold, not warm, weather sudden increases in mortality due to air pollution are unusual and would not be anticipated with the levels recorded. An anonymous report from the State of California Health Department (1956) provides the most impressive evidence that excessive heat is much more lethal than high levels of air pollution. During the last 6 months of 1955 there was a complete lack of correspondence between days of air pollution and deaths in the nursing home population and of persons 65 years of age or older, but during a short 4-day heat wave at the beginning of September there was a 5-fold increase over the maximum number of deaths recorded on any other day.

In Washington, D. C. the temperatures and humidity at the National Airport were similar to those recorded in Central Park (NOAA, 1970B) but the numbers of daily deaths showed no excess above average for the month. Air pollution levels were lower than in New York but more important differences probably lay in the more numerous areas of high building concentrations and population densities which result in heat islands in New York City with higher air temperatures and humidity and more stagnant air conditions than would be recorded in most parts of Washington. High figures for air pollution generally indicate stagnation of air and as these figures were higher in New York than in Washington it is likely that natural ventilation in the former was less satisfactory.

In addition, the New York community had probably lost its summer acclimatization to a greater degree than the population in the District of Columbia. During the first 21 days in New York, daily maxima only reached 87°F (30.6°) on 2 days and 91°F (32.8°) on 1 day; the associated minima being 74°F (23.3°) on 2 days and 70°F (21.1°) on 1 day, maximum temperatures lying in the 50s, 60s or 70s for the remaining 18 days and minimum temperatures in the 50s and 60s, whereas September 1970 was one of the hottest Septembers ever in the Washington area, averaging 5.5°F (3.1°) above normal and most weather stations recorded their hottest readings of the year, many having more days in September than in August with maxima exceeding 90°F (32.2°) (NOAA, 1971). The maximum daily temperature was 80°F (26.7°) or more on 17 of the first 21 days of the month and 90°F (32.2°) or more on 4 of these days. The minimum daily temperature did not fall below 70°F (21.1°) on 7 days. Thus, the population of the Washington area probably became more acclimatized to heat than they had been earlier in the summer and an excess number of daily deaths from heat-aggravated illness would not be expected towards the end of a month when the temperature conditions were uniformly high. The average daily numbers of deaths in the District of Columbia during September were less than in any other month, except May and August, which does not suggest that the overall mortality was increased by the hot weather in the nation's capital in contrast with New York (Fuentes, 1971).

The President's Council on Environmental Quality in its first Report (1970) focusses on the avoidance of pollution of the air, land, sea or waterways but does not refer to the associated requirements for controlling the thermal environment. A Joint Task Force of the United States Public Health Service, the National Institutes of Health and the National Institute of Environmental Health Sciences on Research Planning in Environmental Health Sciences (1970) recognized, however, that there is today a considerable thermal hazard to life of unknown proportions, thus:

> *. . . with the fragmentary data available, it is clear that every year thousands of people die and many more suffer from thermal exposure in the United States. Public health standards for thermal exposure do not exist to assist in the planning of preventive measures.*

More recently, Hardin (1971), in an editorial in *Science*, hammers home the need for a reevaluation of priorities:

> *What will we say when the power shuts down some fine summer on our eastern seaboard and several thousand people die of heat prostration? Will we blame the weather? Or the power companies for not building enough generators? Or the econuts for insisting on pollution controls?*

It is necessary to determine when and where climate control—costly to the economy and the power resources—is necessary to preserve health and life. The aged, the very young, the sick and infirm are more adversely affected by climatic extremes than the young and healthy, especially when they are unacclimatized to warmer conditions than those to which they are accustomed, but the effects are felt by all. It may be asked—how big is the problem? What provision for climate control should be made in hospitals, convalescent homes, nursing homes or homes for the elderly in those parts of the country which must contend with intolerable heat from time to time? What advice, guidance or assistance should be given to federal, state and municipal authorities, private householders, industrialists, business men, doctors and others? Which states are most at risk? What are the priorities for locating new power stations or for supplementing existing power supplies? Which ways of controlling the climate or offsetting its effects are most appropriate? Is partial or complete air-conditioning always necessary or can the situation be handled satisfactorily and more economically, and possibly more healthily, in certain areas by careful location, orientation and construction of dwellings and public buildings, adequate insulation and the use of ceiling or attic fans to increase air movement?

This account of mortality from acute heat illness in the United States and a preliminary attempt to identify other disease groups for which mortality increases when the disease process is aggravated by unseasonal warmth was undertaken to answer some of these questions. It is concerned primarily with the disorders underlined below:

Heat stroke (N992.0)
Heat syncope (N992.1)
Heat cramps (N992.2)

Heat exhaustion (N992.3,4,5)

Heat fatigue, transient (N992.6)
Heat oedema (N992.7)
Other heat effects (N992.9) [ICD, 1965]
Heat-aggravated illnesses

Heat-aggravated illnesses are not included in the International Classification of Diseases. They comprise a large group of mixed cases of heat illness, often reported under the primary diagnosis not as due to the effects of excessive heat, and of other diseases which do not terminate in acute heat illness but where death is hastened or precipitated by excessive warmth.

Mortality was selected for study rather than morbidity because the latter is far less definite than mortality and represents a dynamic rather than a static phenomenon. The occurrence of death is a definite event and the number of such events can be counted. An illness, on the other hand, varies from a minor deviation from normal health which does not interfere with the performance of regular duties or activities, to the chronic case which calls for bedside or custodial care for an indefinite period. Furthermore, an individual afflicted with a disease may experience only one period of illness during the interval of observation, or may have repeated illnesses from the same disease. In addition, during the same period of illness, an individual may suffer from two or more distinct diseases. Thus, the basic problem as to what is to be counted becomes very complex, and the application of the International Classification of Diseases to morbidity statistics cannot be laid down as precisely as for mortality (World Health Organization, 1957).

DEATHS FROM HEAT IN THE FIRST HALF OF THE TWENTIETH CENTURY

It is the exception rather than the rule for the medical effects of heat waves to be reported with precision. In the 19th century the mortality figures for heat deaths were often hopelessly mixed up with the coincident mortality from cholera, dysentery and other infections, as reported (Reyburn, 1855) during the excessively hot summer in St. Louis in 1854. The death toll in one month was roughly comparable with the annual death rate today. Even in the early 20th century, prior to the introduction of large-scale refrigeration for the preservation of food, the downward trend in mortality rates with milder weather in the spring was distorted by peaks in the hot summer months due to alimentary tract infections—babies and infants comprising many of the victims—a relatively minor cause of death nowadays.

There were extensive heat waves in 1901, 1911, 1916 and 1917, some of which may have been more severe than the heat waves which have occurred during the past 20 years. Sporadic and more localized heat waves occurred in other years. Epidemiological data is incomplete, however, clinical accounts are rare and it is only possible to hazard a guess at the overall effect on mortality and morbidity for certain states such as Massachusetts in 1911 which were the subject of special study. The mortality elsewhere was undoubtedly very high at times. In one

isolated account Gauss and Meyer (1917) described the clinical features of 158 heat-stroke cases admitted to Cook County Hospital, Chicago in July 1916 of whom 58 died.

More precise information was provided by Shattuck and Hilferty (1932), who compared the average death rates for heat illness for the years 1919–1928 in the Registration Area which at that time only included about two-thirds of the states. The states with the highest average rates—0.70–1.52/100,000—were Ohio, Michigan, Kansas, Missouri, California, Pennsylvania, New Jersey, Maryland and Delaware, with the next highest rates—0.52–0.69/100,000—Massachusetts, Virginia, Louisiana, New York, the District of Columbia, New Hampshire, Illinois and Connecticut, with rates of 0.38–0.51/100,000—Mississippi, Florida, Tennessee, Kentucky, Wisconsin, Rhode Island and Indiana and with the lowest average rates—0.37/100,000 or less—Colorado, Washington, Utah, Montana, Oregon, North Carolina, Vermont, South Carolina, Maine and Minnesota. The geographic distribution of deaths from excessive heat varied from year to year and death rates in urban areas were higher than in rural areas. Mortality from excessive heat was relatively high during the first year of life, low thereafter up to the age of 20, rose gradually up to the age of 70 and increased sharply after 70 years of age. Mortality among males and females was about equal under 20 and over 70 but between 20 and 70 years of age the death rate for males was about 3 times that for females. Unusually high air temperatures persisting for several days at a time, rather than unusually high humidity or low wind velocity, caused heat deaths. During the 10 years 4,434 males and 1,726 females were certified to have died from the effects of excessive heat in the Registration States alone, annual rates of 0.91 and 0.37 per 100,000 respectively. The death rate per 100,000 was 0.38 for the white and 0.91 for the nonwhite populace.

A further analysis of death certificates in Massachusetts for 1911 by Shattuck and Hilferty (1933) revealed that death rates from heat effects increased markedly with increase in the size of a city. Among the diseases associated with heat as a cause of death diseases of the circulatory system topped the list by a large margin. Excessive heat was as important a cause of death as diphtheria and croup (total deaths 563), diabetes (631), Bright's disease (650), abdominal tuberculosis (586) and senile debility (576).

The third significant contribution by these authors (Shattuck and Hilferty, 1936) was a review of mortality from heat in the world as a whole. The numbers of heat deaths in the United States in 33 years, 1900–1932, exceeded the numbers in all other countries for which figures were available. The death rate in the United States (1.78/100,000) was only exceeded by the rates for the Resident Foreign Community in Shanghai (5.8) and the Republic of Panama (4.4), although it was approached by the average death rate from heat illness in Australia from 1908–1931 (1.49).

Mary Gover (1938) extended these observations to cover mortality from all causes during periods of excessive temperature for 86 large cities in the United States between 1925 and 1937 and observed:

> *Mortality which is certified and recorded as due to 'excessive heat' includes by no means all excess deaths which occur during periods of extreme temperature. During July 1934 in Kansas, 'excessive heat' accounted for only about one-quarter*

of the excess deaths which occurred that month. The remainder of the excess was distributed largely among diseases of the heart, cerebral hemorrhage, nephritis and pneumonia.

In five of the thirteen years from 1925–1937, summer weekly rates of mortality in large cities rose as high as, or higher than, an average January rate. In at least three of the remaining seven years smaller increases in mortality occurred.

These sharp increases in mortality occur most frequently during the month of July, but sometimes they occur in June or August. The area most often affected is roughly outlined by the States of Ohio, Indiana, Illinois, Missouri, Iowa and Nebraska. The more northern states of Michigan, Wisconsin and Minnesota, however, are sometimes a part of the affected area. The North Atlantic cities also frequently experience these sudden increases in mortality. The areas least frequently affected are the far South and the Pacific coast.

Daily maximum temperatures for groups of cities and for individual cities in affected areas show that the excess in mortality is preceded by at least several successive days of extreme temperature. Excess mortality during a second period of extreme temperature in any one year is slight when compared with the excess mortality during the first major heat wave of the summer, even when the second rise in temperature is extreme.

There have been no further comprehensive reviews of this calibre since this paper was published.

Brown (1935) reported the heat wave in Kansas in June, July, and August 1934 in more detail. The maximum daily temperature ranged from 100°F (37.8°) to 111°F (43.9°) from the last 10 days of June to the 3rd week in August with only two brief respites and many of the 291 deaths occurred when it was consistently above 106°F (47.1°). With the exception of 1931 when there were 74 heat deaths, 1930 when there were 65 and 1913 when there were 46, 30 was the largest number of deaths certified to be due to heat in Kansas in the previous 23 years.

In some areas the heat wave in 1936 was even more severe. In Detroit, during the week ending 18 July, the numbers of deaths from all causes were 204% above the average for the preceding 5 years (Root, 1937). The maximum daily temperature exceeded 100°F (37.8°) for 7 days, reaching 104°F (40°) on one day. In the previous 64 years 100°F (37.8°) was only exceeded 7 times. The sporadic character of severe heat waves was illustrated again. Only 17 deaths were certified to be due to heat on the average each year for the previous 15 years, ranging from 0 in 1920 to 40 in 1931, but in July 1936 there had been 304 heat deaths by the 23rd of the month.

Ferris, Blankenhorn, Robinson and Cullen (1938) described the epidemiological and clinical features of 44 heat-stroke cases admitted to Cincinnati General Hospital in July 1936, 17 of whom died. During the first of two heat waves when there were 42 admissions the maximum temperatures recorded by the United States Weather Bureau ranged from 102–106°F (38.9–41.1°) for 8 days.

As far as can be ascertained the 1940s were less troubled with widespread heat waves (United States Weather Bureau Reports 1940–1949) although deaths from heatstroke in the young and the old were reported in New York City during a sharp spell of hot weather in the latter half of August 1948 (Friedfeld, 1949A,B; Cardullo, 1949; Kessler and Andersen, 1951) and in 1949, the first year when deaths from excessive heat and insolation were reincluded in the General

Mortality Tables of the annual Vital Statistics Reports of the United States, 488 deaths were coded under this rubric, well above the average numbers for subsequent years.

During World War II many deaths from heat stroke occurred in the Armed Forces in camps in the United States but it was notable that fatalities associated with heavy exercise occurred not infrequently at relatively low temperatures when the total heat stress was underestimated (Schickele, 1947), not during abnormally hot weather.

HEAT DEATHS IN THE SECOND HALF OF THE TWENTIETH CENTURY

Although deaths due to excessive heat were less frequent, a high incidence of heat illness in the Armed Forces was still reported in the United States during the postwar years. The marked discrepancy between the numbers of cases of heat exhaustion and heat stroke abstracted by Ellis (1955) from the statistical records in the Offices of the Surgeons' General of the United States Army and Navy and the very much larger numbers reported by Cook (1955) from direct interrogation of the Command and Medical Departments of 9 Army camps underlines how very much more common incapacitating heat disorders were than the official records indicated.

The more recent development of the Wet-bulb Globe-thermometer Index (Yaglou, 1956) for measuring and assessing the effects of the thermal environment in the field and the subsequent use of the Index to identify the levels of warmth at which training or other strenuous outdoor activities should be modified or suspended altogether greatly reduced the incidence of heat illness and its prevention has now become a matter of day-to-day military discipline (Yaglou and Minard, 1957; Minard, Belding, and Kingston, 1957; Minard, 1961; Department of Defence, 1969).

The development of the Discomfort or Temperature-Humidity Index (Thom, 1957) was another attempt to link the effects of air temperature and humidity in a single term to predict cooling requirements from measurements made at meteorological stations and it is mentioned not infrequently on radio and television. It is not used, however, to warn the civil populace of the levels of warmth at which to modify its activities, or to reduce the heat load in other ways by wearing less clothing, encouraging air movement and the optimum use of air-conditioning, and to keep fully hydrated.

Since World War II, the growth of refrigerated food storage and antibiotic and chemotherapeutic advances have reduced to negligible proportions the mortality from many lethal infectious diseases which formerly overshadowed the mortality statistics for climatic stress during the summer months. Kutschenreuter (1959) plotted the average seasonal mortality curves for New York City from monthly totals of mortality reported for all age groups for the years 1949–1958 and the mean monthly normal temperature curves for the years 1921–1950. The average daily mortality fell from a maximum of about 245 in January to a minimum of about 192 in August as the average daily temperature rose from 30°F (−1.1°) to 75°F (23.0°) and then increased during the autumn months until

the following January. It was notable, however, that the improving trend observed in the spring months was arrested temporarily in May and June when the mortality curve flattened before continuing its decline during July and August. Similar, but rather less consistent, annual mortality curves in relation to air temperature are shown for Los Angeles and Cincinnati for the same periods. He also plotted the month-by-month mortality curves for different age groups. The trend for all age groups was again apparent for persons of 25 years of age or older and for infants under 1 year of age but not for children and young adults between the ages of 1 and 24 who were apparently more resistant to seasonal change.

Oechsli and Buechley (1970) analyzed copies of death certificates for persons aged 50 or over in Los Angeles and Orange Counties from 21 August to 10 October 1939, 1955 and 1963, when heat waves with temperatures well in excess of 100°F (37.8°) occurred during the month of September and for a control year, 1947. They concluded that excess mortality due to heat must be estimated on total mortality from all causes since certification of deaths due to excess heat was rare. There were 546 excess deaths in 1939, 946 in 1955 and 580 in 1963 which, in the authors' opinion, resulted from the effects of heat. They found little effect of temperature on mortality with maximum temperatures under 95°F (35°) but experience in New York in September 1970 and elsewhere suggests that this may not be universally true. Practically no deaths were certified to be due to heat as Kutschenreuter (1959) observed for New York. The daily number of deaths increased with increasing temperatures and advancing age and there was a time lag of one day between the maximum daily temperature and the maximum daily mortality, as Kutschenreuter also found. There was no evidence of any deviation

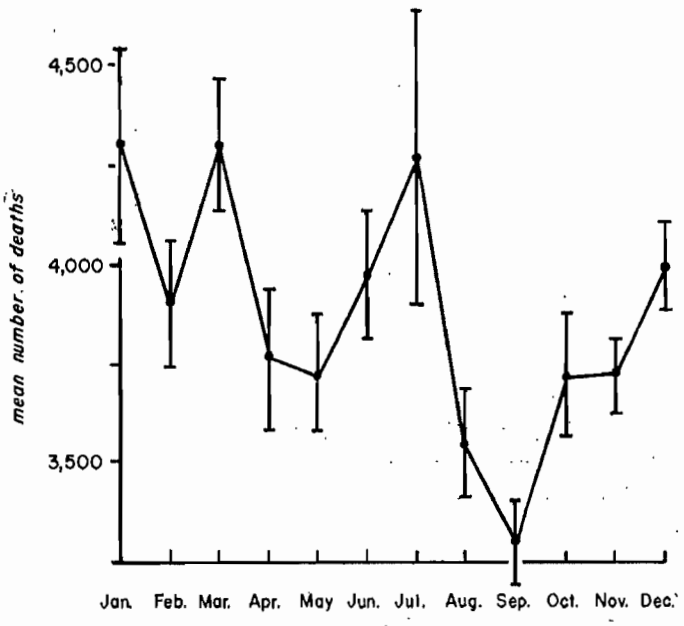


FIG. 1. Deaths from all causes, Missouri, 1952–1955, 1966.

from expected mortality in the control year 1947. The longest of these heat waves only lasted 7 days and the shortest 4 days but they were associated with a considerable increase in the daily mortality. In 1955 an initial peak temperature of 110°F was followed next day by an increase of 445% over the expected numbers of deaths of persons over 65 years of age, the disaster reported by the California Department of Health already cited, and to these frightening numbers must be added the unknown number of excess deaths of persons under 65. The main objective of this study was to develop a formula for predicting the age-specific mortality ratio. The prediction worked well for a subsequent heat wave in 1955 but the fit for 1963 suggested that an earlier hot spell during the summer and/or increased installation of air-conditioning in nursing homes and private homes during the intervening 8 years had reduced the mortality from heat. This trend has continued and for the past 5 years the California Health Department has ceased to monitor heat deaths in nursing homes.

St. Louis, Missouri, has suffered repeatedly from heat waves over the years. Austin and Berry (1956) reported 100 selected cases of heat stroke from more than 1,000 patients observed in the receiving room of the St. Louis City Hospital for the years 1952, 1953 and 1954—three of the hottest summers on record. The average impact on deaths from all causes in the state of Missouri of 5 years, 1952–1955 and 1966, when the certified heat deaths in the United States exceeded 500, is illustrated in Fig. 1. The average number of deaths in July nearly equal the average number in January. The numbers of deaths for each year in Table I paint an even more alarming picture. In July 1966 there were 5,530 deaths from all causes in Missouri, 1,507 more than in June and 1,588 more than in August and more deaths than in any other month in this 5-year period.

Henschel, Burton, Margolies and Smith (1969) analyzed 1,428 death certificates for the City of St. Louis for the greater part of July 1966. Heat was certified to be the primary cause of death on 246 certificates and a contributing factor on another 40. In other words, excessive heat was the primary or secondary cause of death for one-fifth of all those who died that month and the excess numbers of deaths from all causes for the state as a whole suggests that the true death toll was even greater than this. Schuman (1967) reported that there were 570 excess deaths from all causes in the city during July 1966 as compared to July 1965. One older census tract had 266% more deaths in 1966 than in 1965, whereas in two other areas with better housing and higher income groups there were actually smaller numbers of deaths in 1966 than 1965, while in the other 23 census tracts there were on average 84% more than the expected number of deaths during this prolonged heat wave. The maximum daily temperatures were above 90°F (32.2°) for 24 out of 28 days and above 100°F (37.8°) on 7 days.

Hardy (1971), concluding an address to the American Society of Heating, Refrigerating and Air-Conditioning Engineers in 1969, remarked "Thermal exposures in the United States today result in significant increases in morbidity and mortality among all ages but particularly in the age group 65 years and older." He cited the observations of Bridger and Helfand (1968) on mortality in Illinois during July 1966 where the heat wave was less severe than in Missouri.

TABLE I

DEATHS FROM ALL CAUSES FOR MISSOURI, BY MONTH: 1952, 1953, 1954, 1955, 1966

Year	Jan.–Dec. (incl.)	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.
1952	45,111	4,044	3,845	4,153	3,635	3,613	**4,441**	3,618	3,268	3,253	3,696	3,612	3,933
1953	45,689	5,024	4,058	4,009	3,753	3,721	**3,893**	3,656	3,536	3,243	3,426	3,551	3,819
1954	44,392	3,969	3,357	3,814	3,576	3,549	3,999	**4,734**	3,284	3,103	3,544	3,604	3,859
1955	43,505	3,760	3,571	3,681	3,497	3,432	3,407	**3,877**	**3,750**	3,167	3,601	3,767	3,995
1966	52,472	4,741	4,217	4,662	4,448	4,311	4,023	**5,530**	3,942	3,727	4,335	4,082	4,454
Mean	46,234	4,308	3,810	4,064	3,784	3,725	3,953	**4,283**	3,556	3,299	3,720	3,723	4,012

Only 70 deaths were reported to be due to heat but the deaths from all causes were 13.6% or 1,148 deaths more numerous than would have been expected from previous experience in July 1965.

The annual Vital Statistics Report for Illinois for 1966 indicates the localized nature of this heat wave. There were 1,872 deaths in July 1966 in 32 counties lying on either side of a line from Alton in Madison County, on the other side of the Mississippi from St. Louis and near to the confluence of the Missouri and the Mississippi, to Danville in Vermilion County. This represented a 35% increase in deaths compared to the numbers in July 1965. A feature of the heat wave was that although the highest daily maximum temperature at the Alton Dam Weather Station occurred towards the end of the 2nd week, the maximum daily minimum temperature of 82°F (27.8°), which was unusually high for Illinois, did not occur until a week later. Information is not available in the report on the distribution of heat deaths during the period of the heat wave which might have thrown some light on the relative importance of daily maximum and minimum temperatures. This was not the worst heat wave in Illinois. In July 1936 there were 9,423 deaths in contrast with 6,727 deaths in July 1935 and the number of fatalities from heart disease, apoplexy, nephritis, cancer and diabetes was 4,013 higher. The increase in infant deaths was 20%. These investigators considered that the especially dangerous periods of the year were first during the sudden rise in temperature either in late May or early June before people had an opportunity to adjust to the increment in environmental warmth and, second, the period when temperature and humidity indices showed that the thermal conditions were in the heat-stroke danger zone which they defined as 24-hour average air temperatures above 90°F (32°) or 24-hour Temperature-Humidity Indices (Thom, 1957) above 81°F (27°). They commented that the first dangerous period occurred every year but that the 2nd period might occur on consecutive years or it might not appear for several years. Helfand and Bridger (1971) extended their investigations to 10 other eastern and midwestern states and report in a paper which is in the press "in these few states only, there were 6,699 (11.5%) more deaths in July 1966 than on average for July in the preceding three years. Deaths from stroke alone were 1,041 (16.7%) above the preceding three-year July average." These observations confirmed the findings of Schuman, Andersen and Oliver (1964) in Detroit, Michigan, who also reported that there was a considerable increase in the numbers of deaths from cerebrovascular accidents during excessively warm weather.

Heat stroke continues to be an endemic disease in New York City in the summer months. Ferguson and O'Brien (1960) reported deaths from this cause every year from 1948–1959, 61 deaths occurring in 1952, while Levine (1969) reported 200 patients seen at the King's County Hospital, Brooklyn in the 1966 July heat wave, 25 of whom died, only 3 being less than 70 years of age. The increased numbers of deaths from all causes in July 1966 (Buechley, 1971A; Schuman, 1967) also support this evidence that excessive environmental warmth continues to threaten life in this City. Buechley found that the number of deaths in July 1966 were more than twice the expected numbers in the hot core of the New York–New Jersey metropolitan area and were less than twice the expected num-

bers in the cooler suburbs. He reported that air temperatures, especially the night time minima, were 10°F higher in the urban core. There were 1,020 deaths in the entire New York–New Jersey area on the 4th of July, an excess of 539 over the number normally expected for this area on a July day. Over a 2-week period which included the 4th of July, Schuman (1967) reported that there were 1,181 excess deaths in New York City. The leading causes of the excess deaths were arteriosclerotic heart disease, including coronary disease (490), respiratory diseases and influenza (160), cancer [127], cerebrovascular accidents (76), diabetes (62), accidents and homicides (52). The number of suicides were 15 below the expected number. The numbers of deaths were highest in Brooklyn and Queens and lowest in the Bronx and Manhattan. He concluded that the striking differences in mortality in adjacent census tracts in large cities were more likely to be due to differences in the population at risk rather than to meteorological differences alone and that unless something was done to supplement incomes and to provide air-conditioning and adequate medical care, or to facilitate the escape of those who were most vulnerable to the cooler country air, heat stress would continue to exact a heavy toll among the aged and those with cardiovascular diseases. In Philadelphia the numbers of deaths on 3, 4 and 5 July 1966 were also more than double the expected numbers which suggests that this city was hit equally as hard as New York by the heat wave (Buechley, 1971B).

These accounts indicate the sporadic nature of epidemics of acute heat illness in time and location. They further underline the fact that the number of deaths which are certified to be due to excessive heat constitute only a small proportion of the deaths from other disorders which are precipitated or aggravated in severity by excessive heat. Certification of these to other causes means that they are not counted as heat deaths. The contemporary picture is, however, far from complete and a cursory review of the meteorological tables (United States Weather Bureau Reports, 1900–1967) prompts the uneasy thought that deaths due to excessive warmth may have occurred more frequently than is generally realized in some parts of the country in most years.

THE VITAL STATISTICS OF THE UNITED STATES 1952–1967

Fortunately, the number of deaths certified to be due to "excessive heat and insolation (E931)" "by month" have been included since 1952—the first of 4 severe heat-wave years in the 1950s—in the General Mortality Tables of the United States Vital Statistics Reports, which permits the seasonal pattern of certified/coded heat illness to be studied at the national level for the first time. In these tables the nomenclature of the Sixth Revision of the International Classification of Diseases (1949) was used from 1949–1957 and that of the Seventh Revision (1957) for the subsequent years up to and including 1967—the last year for which these Reports are available at present. With certain exceptions, to which reference is made, the Seventh Revision does not qualify the comparisons made below.

The seasonal trends may be compared with the average monthly mortality indices for all causes for the decade 1951–1960, adjusted for seasonal variation and epidemic excess, according to Rosenwaike (1966) in Fig. 2. Rosenwaike as-

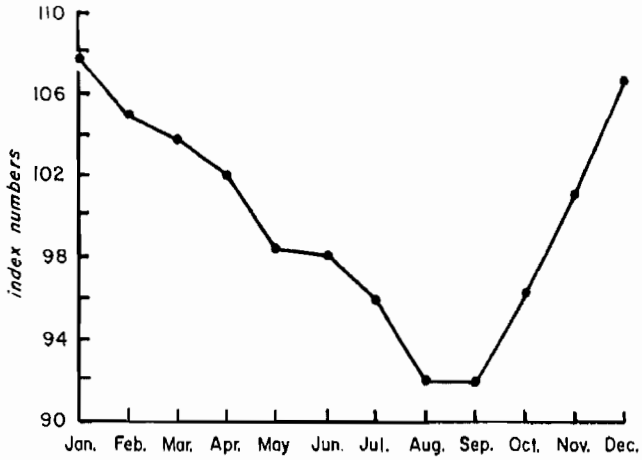


FIG. 2. Seasonal variations in deaths, all causes, U. S. A., 1951–1960.

sumed that ratios of the original observations to a 12-month moving average included the seasonal and erratic components but not the trend and cyclical components and that averages of the ratios for each of the 12 months measured the seasonal component alone. The seasonal indices for death rates were prepared by the United States Bureau of the Census, utilizing "Census Method II"—an elaboration of the ratio-to-moving-average method. The resultant pattern is one of a steady decline in the average mortality from the winter months until August and September, after which the mortality rises again until the end of the

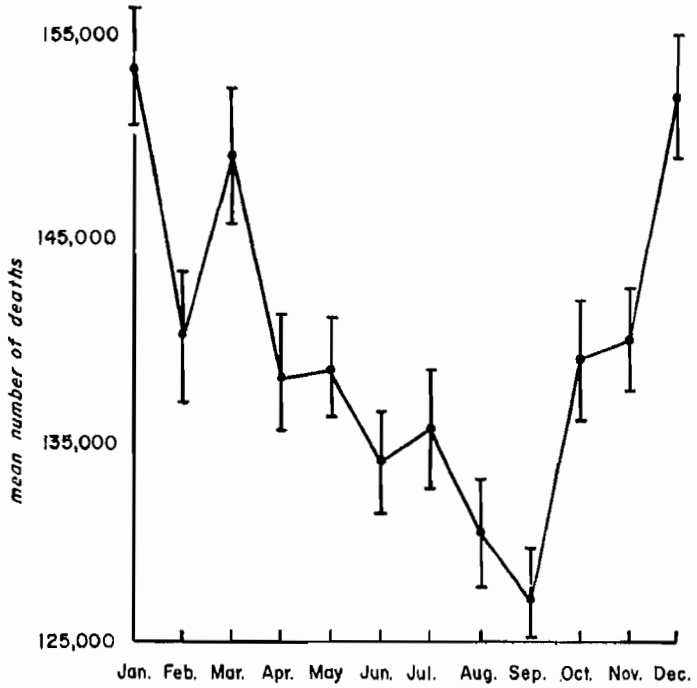


FIG. 3. Deaths from all causes, U. S. A., 1952–1967.

year. The June–July kink in the downward mortality curve was more apparent in Kutschenreuter's uncorrected curves for the years 1949–1958 and suggests that the mortality pattern was modified in some way during these months.

Deaths from All Causes

The mean numbers of deaths from all causes, by month, for the years 1952–1967 and the standard errors of the means are plotted in Fig. 3. If it were not for peaks in March, May and October, probably largely due to differences in the numbers of days in each month, the most notable deviation from Rosenwaike's smooth curve is the peak in July. The numbers of deaths in July in Table II for 10 of these years were appreciably greater than in June, August or September. The largest number of "excess deaths"—the average of the differences between the numbers of deaths in the months preceding and the months following the month with the greatest numbers of deaths from heat and insolation—was recorded in 1966 when there were 159,924 deaths in July compared with 149,251 deaths in June and 145,184 deaths in August, while in 1955 there were 130,730 deaths in July, 119,598 in June and 122,858 deaths in August.

Deaths from All Causes and from Excessive Heat and Insolation

The mean number of deaths from all causes and from excessive heat and insolation for the United States for 5 years when the total number of deaths from heat exceeded 300 per annum—1952–1955 and 1966—are shown in Fig. 4, together with the standard errors of the means and the annual figures are given in Table III. The maximum deaths from heat and insolation occurred in July and there is a close correspondence between the mean numbers of deaths in this month and August and September and those for deaths from all causes. The pattern differed from year to year. In one year, 1966, the great majority of deaths from heat were concentrated in the single month of July. In 3 years—1952, 1954, and 1955—when the heat deaths were spread over 3 or 4 months, the excess deaths in the month with the greatest number of heat deaths was always less than in 1966. In 1953, when there was no great concentration of heat deaths in any one month but appreciable numbers occurred from May to September, no excess deaths from all causes were identifiable during the summer months.

The rather greater excess number of deaths from all causes in the months when there were most heat deaths over the numbers in the following months compared to the excess over the preceding months in 1952, 1954, 1955 and 1966 could be due in part to the resumption of the normal seasonal pattern after the heat wave and in part to an unduly large mortality from various causes among the more fragile members of the community during the heat wave months.

The mean number of deaths from all causes and from excessive heat and insolation from May to September in the 11 years when the total heat deaths were less than 300 per annum are plotted in Fig. 5 and the annual figures are tabulated in Table IV. The figures indicate that even when there was not a severe heat wave there was a small excess of deaths from heat and insolation in July which coincided with a similar excess in the number of deaths from all causes in

TABLE II

DEATHS FROM ALL CAUSES FOR THE UNITED STATES, BOTH SEXES, ALL RACES, BY MONTH: 1952-1967

Year	Jan.–Dec. (incl.)	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.
1952	1,496,838	132,784	126,322	138,487	124,977	123,246	**127,427**	120,516	112,914	116,581	123,998	123,109	132,477
1953	1,517,541	147,304	137,314	132,450	123,586	124,480	122,995	118,877	117,050	115,952	120,798	123,209	133,728
1954	1,481,091	136,016	117,020	128,011	121,148	124,492	121,389	**124,203**	113,673	112,290	121,734	124,996	136,119
1955	1,528,717	137,487	125,920	130,508	125,188	125,756	119,598	**130,730**	122,858	115,330	125,697	128,863	140,962
1956	1,564,476	141,454	128,654	139,496	131,936	130,261	126,328	123,261	123,720	120,061	128,363	139,856	140,086
1957	1,633,128	145,338	125,852	140,363	132,151	131,920	131,698	131,610	124,433	123,536	148,985	148,487	148,755
1958	1,647,886	156,658	147,494	148,211	135,585	133,940	127,975	**129,194**	125,442	122,915	135,358	134,629	150,485
1959	1,656,814	151,950	131,023	146,931	140,670	139,280	132,861	132,614	133,325	126,087	134,257	139,072	148,744
1960	1,711,982	163,833	158,754	153,997	136,415	138,786	132,461	133,372	130,004	128,012	141,073	139,513	155,762
1961	1,701,522	153,942	136,268	144,788	141,426	141,434	135,768	**138,833**	134,014	132,252	143,225	142,427	157,145
1962	1,756,720	163,043	**145,450**	157,564	146,081	145,923	136,557	**139,301**	**138,371**	123,417	145,250	145,622	160,141
1963	1,813,549	165,843	161,099	176,287	147,674	145,934	143,523	**144,493**	137,149	135,584	145,083	144,206	166,404
1964	1,798,051	163,230	147,295	156,485	145,168	148,832	146,198	**148,602**	143,487	137,161	152,158	148,104	161,322
1965	1,828,136	164,856	153,574	165,064	150,285	150,759	144,288	**146,784**	143,279	139,821	153,031	152,106	164,289
1966	1,863,149	166,766	151,296	164,804	158,913	156,455	149,251	**159,924**	145,184	141,164	154,777	150,678	163,882
1967	1,851,323	164,434	147,997	161,194	150,379	156,406	147,199	**149,767**	146,488	144,669	154,460	155,913	172,414
Mean	1,678,182	153,434	140,083	149,040	138,223	138,619	134,094	**135,761**	130,711	127,187	139,264	140,038	152,044

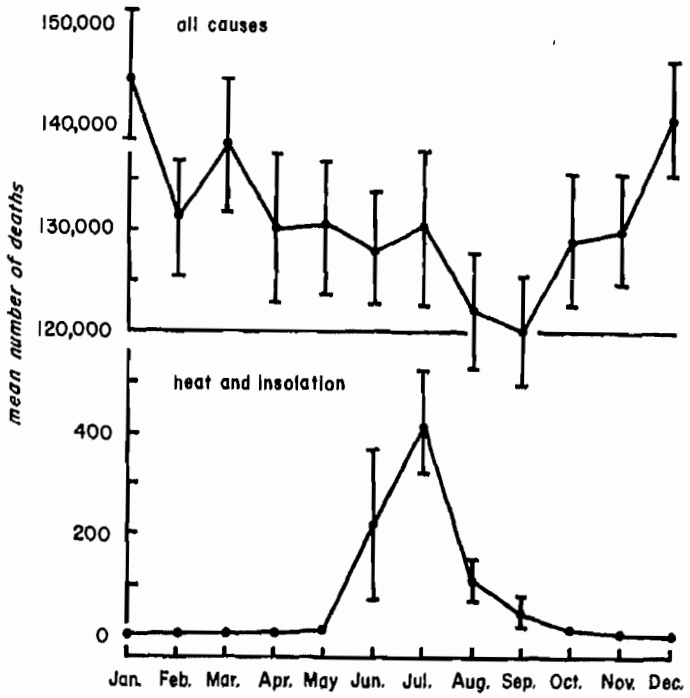


FIG. 4. Total heat deaths greater than 300 per year, U. S. A., 1952–1967.

8 of these 11 years. Some of the relatively small numbers of excess deaths were probably attributable to other than seasonal climatological causes.

VASCULAR LESIONS OF THE CENTRAL NERVOUS SYSTEM

Several observers, including Gover (1938), Ferris *et al.* (1938), Schuman *et al.* (1964), Levine (1969) and Bridger and Helfand (1971), commented that the most common serious pathological condition associated with an increase in the number of deaths during a heat wave is cerebrovascular arteriosclerosis and associated cerebral hemorrhage. In a detailed study of New Haven, Connecticut death certificates at Yale University, Florey, Senter, and Acheson (1967) also observed a rise in the percentage of deaths from cerebrovascular accidents for the years 1959–1964 during July and August, usually the hottest months of the year.

The General Mortality Tables show there was an excess number of deaths from cerebrovascular accidents in the United States as a whole in June 1952 and in July 1954, 1955 and 1966, although this was not apparent in 1953, the year when there was not an excess of deaths from all causes in any of the summer months. The mean numbers of deaths for these 5 years are shown in Fig. 6 with the standard errors of the means and the annual figures are tabulated in Table V. On an average there was an excess of 407 more deaths from stroke in July than in June and an excess of 702 more deaths in July than August. In 1966, the worst year in this respect, there were 1,633 more deaths from strokes in July than

TABLE III

DEATHS FROM ALL CAUSES AND FROM EXCESSIVE HEAT AND INSOLATION (E931), BY MONTH, FOR THE UNITED STATES 1952–1967, FOR YEARS WHEN THE TOTAL HEAT DEATHS WERE IN EXCESS OF 300 PER ANNUM [VITAL STATISTICS OF THE UNITED STATES, VOL. II, UNITED STATES PUBLIC HEALTH SERVICE]

Year		Jan.–Dec. (incl.)	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.
1952	All causes	1,496,838	132,784	126,322	138,487	124,977	123,246	**127,427**	120,516	112,914	116,581	123,998	123,109	132,477
	Heat	1,401	2		4	2	7	**795**	462	90	31	5	1	2
1953	All causes	1,517,541	147,304	137,314	132,450	123,586	124,480	122,995	118,877	117,050	115,952	120,798	123,209	133,728
	Heat	576	1			4	26	181	137	79	138	7	2	1
1954	All causes	1,481,091	136,016	117,020	128,011	121,148	124,492	121,389	**124,203**	113,673	112,290	121,734	124,996	136,119
	Heat	978		2	1	3	4	106	**758**	79	20	3	2	
1955	All causes	1,528,717	137,487	125,920	130,508	125,188	125,756	119,598	**130,730**	122,858	115,330	125,697	128,683	140,962
	Heat	615		2	1	2	3	17	**313**	236	41			
1956	All causes	1,863,149	166,766	151,296	164,804	158,913	156,455	149,251	**159,924**	145,184	141,164	154,777	150,678	163,882
	Heat	531				1	4	32	**451**	29	5	4	1	4
Mean for 5 years	All causes	1,577,467	144,071	131,574	138,852	130,763	130,886	128,132	**130,850**	122,336	120,263	129,401	130,135	141,434
	Heat	820	0.6	0.8	1.2	2.4	8.8	226	**424**	103	47	3.8	1.2	1.4

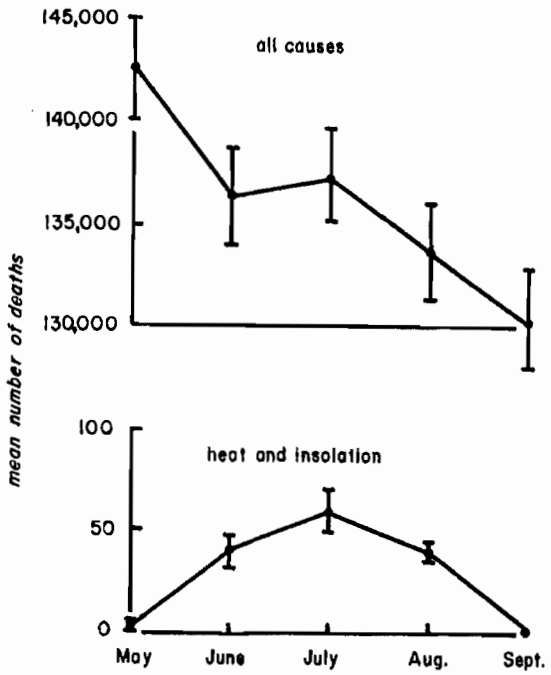


FIG. 5. Total heat deaths less than 300 per year, U. S. A., 1952–1967.

TABLE IV

DEATHS FROM ALL CAUSES AND FROM EXCESSIVE HEAT AND INSOLATION (E931), BY MONTH, FOR THE UNITED STATES, MAY–SEPT. 1952–1967, FOR YEARS WHEN THE TOTAL HEAT DEATHS WERE LESS THAN 300 PER ANNUM [VITAL STATISTICS OF THE UNITED STATES, VOL. II, UNITED STATES PUBLIC HEALTH SERVICE]

Year		Jan.–Dec. (incl.)	May	June	July	August	Sept.
1956	All causes	1,564,476	130,261	126,328	123,261	123,720	120,061
	Heat	174	14	61	13	13	5
1957	All causes	1,633,128	131,920	131,698	131,610	124,433	123,536
	Heat	280	3	94	123	45	7
1958	All causes	1,647,886	133,940	127,975	**129,442**	125,442	122,915
	Heat	137	7	20	**53**	29	12
1959	All causes	1,656,814	139,280	132,861	132,614	133,325	126,087
	Heat	267	13	61	80	79	15
1960	All causes	1,711,982	138,786	132,461	**133,372**	130,004	128,012
	Heat	168	0	35	**55**	34	36
1961	All causes	1,701,522	141,434	135,768	**138,833**	134,014	132,252
	Heat	191	4	60	**59**	36	23
1962	All causes	1,756,720	145,923	136,557	**139,301**	**138,371**	123,417
	Heat	154	8	10	**40**	**68**	9
1963	All causes	1,813,549	145,934	143,523	**144,493**	137,149	135,854
	Heat	196	4	44	**74**	37	23
1964	All causes	1,798,051	148,832	146,198	**148,602**	143,487	137,161
	Heat	195	5	34	**90**	53	5
1965	All causes	1,828,136	150,759	144,288	**146,784**	143,279	139,821
	Heat	106	6	10	**39**	34	5
1967	All causes	1,851,323	156,406	147,199	**149,767**	146,488	144,669
	Heat	96	12	21	**25**	21	6

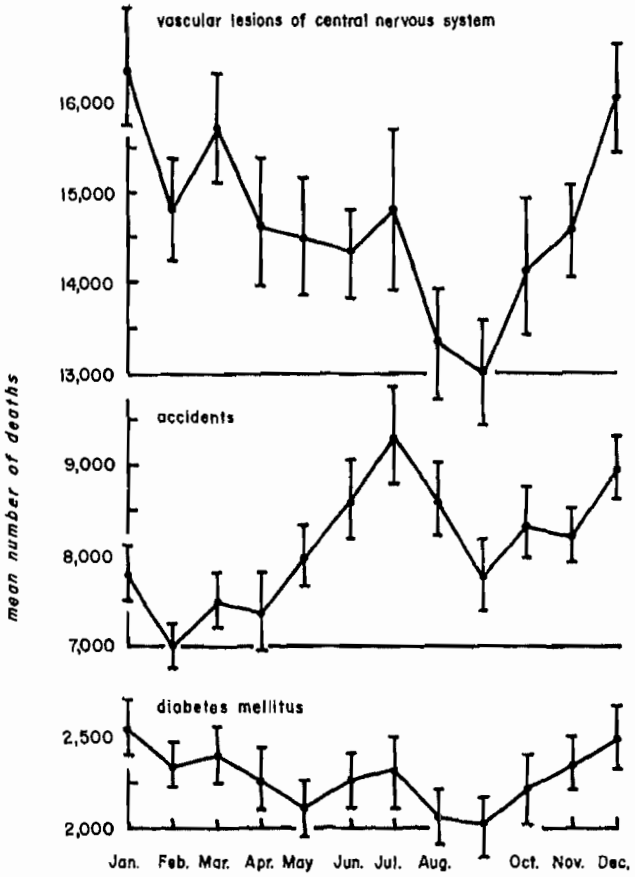


FIG. 6. Years when total heat deaths greater than 300 per year.

in June and 2,540 more than in August. It is difficult to attribute this excess mortality in July to any cause other than the heat waves.

There were also excess numbers of deaths from cerebrovascular accidents in either July or August in 8 out of 11 years when fewer than 300 deaths were coded to be due to heat and insolation.

ACCIDENTS

The number of accidents increases when people work in hot and humid environments. The average seasonal mortality from accidents (E800–E962) is plotted in Fig. 6 and the annual numbers are given in Table V for the 5 years when more than 300 heat deaths were coded. There were more accidental deaths in June or July during these 5 years than in any other month. This, however, is the start of the summer recreational and vacation season and the possibility that nonclimatic causes rather than summer warmth accounted for the increase in the numbers of deaths is supported by increases in deaths from accidents in motor vehicles (E810–E835), accidental falls (E900–E904) and accidental drowning (E929) during the month of July in each of these years.

In 1966 the majority of heat deaths occurred in July. Relatively few deaths

TABLE V

DEATHS FROM VASCULAR LESIONS OF THE CENTRAL NERVOUS SYSTEM (330–334), ACCIDENTS (E800–962) AND DIABETES MELLITUS (260) FOR YEARS WHEN THE TOTAL HEAT DEATHS WERE IN EXCESS OF 300 PER ANNUM

Year	Jan.–Dec. (incl.)	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.
Vascular lesions affecting the central nervous system													
1952	166,331	15,283	14,160	15,459	13,807	13,589	**14,403**	13,280	12,003	11,884	13,582	13,728	15,013
1953	169,800	16,186	15,065	15,384	14,240	13,993	13,981	13,032	12,825	13,091	13,011	13,814	15,178
1954	167,777	15,679	13,407	14,885	13,620	13,925	13,884	**14,493**	12,572	12,218	13,289	14,101	15,764
1955	174,142	15,942	14,679	14,910	14,433	13,952	13,505	**15,372**	13,923	12,675	13,876	14,580	16,295
1966	204,841	18,913	16,908	18,132	17,375	17,128	16,357	**17,990**	15,450	15,181	17,081	16,349	17,977
Accidents													
1952	96,172	7,431	7,018	7,533	7,330	7,806	**9,350**	8,925	8,238	7,546	8,342	8,250	8,403
1953	95,032	7,693	6,888	7,452	7,222	7,954	**8,618**	**8,436**	**8,220**	7,904	8,081	7,907	8,657
1954	90,032	7,527	6,635	6,864	6,647	7,392	7,846	**8,811**	**7,772**	6,967	7,731	7,570	8,270
1955	93,443	7,289	6,501	6,884	6,834	7,716	7,505	**9,040**	**8,659**	7,421	8,284	8,080	9,230
1966	113,563	9,027	7,965	8,599	9,066	9,285	9,793	**11,372**	**10,186**	9,072	9,774	9,312	10,112
Diabetes mellitus													
1952	25,474	2,296	2,193	2,357	2,158	2,028	**2,214**	2,122	1,856	1,814	2,033	2,106	2,297
1953	25,796	2,600	2,356	2,089	2,018	**2,134**	**2,114**	1,977	1,974	1,968	2,051	2,135	2,380
1954	25,151	2,387	1,991	2,189	2,031	2,006	**2,103**	**2,133**	1,845	1,820	2,132	2,169	2,345
1955	25,488	2,318	2,210	2,265	2,133	2,089	1,983	**2,252**	2,001	1,790	2,007	2,095	2,345
1966	34,597	3,106	2,726	2,972	2,920	2,799	2,843	**3,027**	2,645	2,650	2,968	2,851	3,090

were coded to be due to heat in August but the numbers of deaths from falls and automobile accidents in August shown below were very similar to the numbers for July but declined in September when the holiday season came to an end.

	May	June	July	August	September
Motor Vehicles	—	4391	5031	5024	4632
Falls	—	1624	1741	1701	1531
Drownings	655	1113	1351	703	402

Diabetes

The association of diabetes and heat-wave deaths was recognized by Shattuck and Hilferty (1932), Mary Gover (1938), Austin and Berry (1956), Ferguson and O'Brien (1960), Henschel, Burton, Margolies and Smith (1969), Levine (1969) and Green (1967). Schuman (1971B) observed that between 2 and 15 July 1966 in New York City there were 81% more deaths from diabetes during the heat wave than would have been expected from the numbers in May. Green noted that high blood glucose levels were found in a large proportion of supposedly nondiabetic heat-stroke patients, an association which had not been reported previously. In general, the blood glucose levels were highest in the most severe cases of heat stroke and the explanation for this was obscure. It is, however, notable that Shibolet, Coll, Gilat and Sohar (1967), in their exhaustive study of 36 cases of heat stroke in men between 17–24 years of age, did not report glycosuria in a single case.

The average number of deaths from diabetes for the 5 heat-wave years are plotted in Fig. 6 together with the standard errors of the means and the annual figures are given in Table V. The curve, although it does show a rise in the average number of deaths in July, is less convincing than these figures as the maximum numbers of diabetic deaths occurred in May in 1953 when the heat wave started early in the year, in June in 1952 and 1954 and in July in 1955 and 1966. In 5 of the other 11 years there were more diabetic deaths in July than in June or August and in 2 years the "summer Maximum" occurred in May and June. In 4 years there were no seasonal effects. The monthly vital statistics, while they are suggestive, are less meaningful than the clinical and epidemiological evidence which is sufficiently strong to justify the follow-up of older patients in diabetic clinics during the summer months to see if excessively warm spells do have deleterious effects.

Diseases of Early Infancy

A comparison of deaths from selected causes assigned according to the Sixth and Seventh Revisions of the International Lists for a 10% sample of deaths in the United States shows that for "certain diseases of early infancy (760–776)" there were 6,904 deaths according to the Seventh Revision used in the Report for 1958 but only 6,739 according to the Sixth Revision; the provisional comparability ratio being 1.02. The main groups showing increasing numbers of deaths with the use of the Seventh Revision were birth injuries, postnatal asphyxia and atelectasis (760–762), infections of the newborn (763–768) and other diseases peculiar to early infancy and immaturity unqualified (769–776).

The figures were also modified by the reclassification to rubric 773 of hyaline-membrane disease from other diseases of the lung and pleural cavity (527.2) and transfers within certain diseases of early infancy when immaturity and/or other conditions were jointly reported with hyaline-membrane diseases. Categories mainly involved in the transfer were birth injuries, postnatal asphyxia and atelectasis (762), ill-defined diseases peculiar to early infancy (773) and immaturity with mention of any other subsidiary condition (774). Reclassification of a few other terms reported as causes of death for infants resulted in the transfer of cases out of or into rubric 773. While this militates against the use of rubrics 700–760 for comparing the incidence of fatal disorders of early infancy before and after 1958 (including 1958) it does not preclude the use of this large group of infant diseases to examine the effects of changes in infant mortality from month to month over this 16-year period.

The very young are more prone to succumb to the effects of climatic extremes than older persons as they are unable to protect themselves and their thermoregulatory control is less stable. The mean numbers of deaths and the standard errors of the means for "certain diseases peculiar to early infancy (760–776)" for the years 1952–1967 are plotted in Fig. 7. This remarkable curve is the reverse of the normal mortality curve for all causes with the maximum numbers of deaths in the summer and the minimum in the winter. Table VI shows there were more deaths from this broad group of diseases in July than in June or August in each of the 16 years. The most frequent causes of death were coded as birth injuries, postnatal asphyxia and atelectasis, immaturity, pneumonia of the newborn and ill-defined diseases peculiar to early infancy. There were rarely more than 1,000 deaths per annum in any of the remaining disease categories, including diarrhea of the newborn, neonatal diseases arising from certain diseases of the mother during pregnancy and other infections of the newborn. The effect of the Seventh Revision is seen in the increase in the total deaths in 1958, after which infantile mortality was progressively reduced every year.

The mean number of live births for the years 1952–1967 are plotted in Fig. 8.

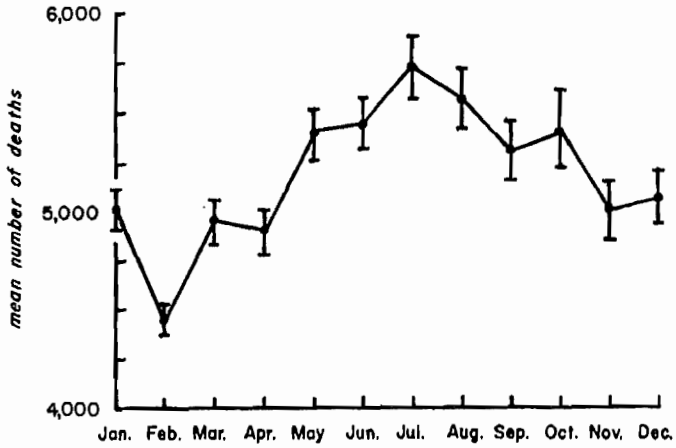


FIG. 7. Deaths from "certain diseases of early infancy," U. S. A., 1952–1967.

TABLE VI

DEATHS FROM "CERTAIN DISEASES OF EARLY INFANCY (760–776)" FOR THE UNITED STATES, BOTH SEXES, ALL RACES, BY MONTH: 1952–1967

Year	Jan.–Dec. (incl.)	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.
1952	63,659	5,088	4,585	4,984	5,043	5,363	5,719	**5,952**	5,647	5,491	5,507	5,031	5,249
1953	63,444	5,168	4,490	4,963	4,877	5,554	5,537	**5,812**	5,701	5,466	5,551	5,084	5,241
1954	63,486	5,096	4,484	4,979	5,077	5,386	5,615	**5,846**	5,782	5,419	5,571	4,992	5,239
1955	64,043	5,064	4,589	5,088	5,006	5,514	5,603	**5,764**	5,754	5,618	5,462	5,294	5,287
1956	64,546	5,027	4,705	4,994	5,078	5,498	5,638	**6,020**	5,990	5,324	5,637	5,247	5,388
1957	66,569	5,232	4,726	5,348	5,282	5,736	5,865	**6,279**	5,957	5,583	5,847	5,380	5,334
1958	68,960	5,471	4,759	5,550	5,380	5,934	5,881	**6,324**	6,221	5,893	6,059	5,746	5,742
1959	67,934	5,585	4,874	5,425	5,354	5,963	5,849	**6,162**	6,158	5,824	5,758	5,397	5,585
1960	67,094	5,342	4,925	5,232	5,285	5,849	5,808	**6,002**	5,857	5,611	5,989	5,466	5,728
1961	65,679	5,415	4,637	5,281	5,220	5,538	5,608	**5,911**	**5,924**	5,655	5,649	5,380	5,461
1962	64,205	5,267	4,632	5,204	5,062	5,564	5,669	**5,789**	**5,703**	5,463	5,426	5,124	5,302
1963	62,688	5,040	4,641	5,067	5,014	5,543	5,338	**5,704**	5,573	5,316	5,388	5,005	5,059
1964	60,322	4,797	4,449	4,839	4,708	5,299	5,420	**5,645**	5,386	5,104	4,970	4,874	4,831
1965	55,398	4,659	4,094	4,645	4,507	4,928	4,946	**5,025**	4,874	4,557	4,556	4,248	4,359
1966	51,644	4,223	3,715	4,222	4,075	4,503	4,502	**4,720**	4,693	4,362	4,364	3,973	4,292
1967	48,314	3,958	3,540	3,918	3,968	4,299	4,143	**4,462**	4,308	3,941	3,991	3,923	3,863
Mean	62374.	5027.	4490.	4983.	4933.	5404.	5446.	**5713.**	5595.	5289.	5357.	5010.	5122.

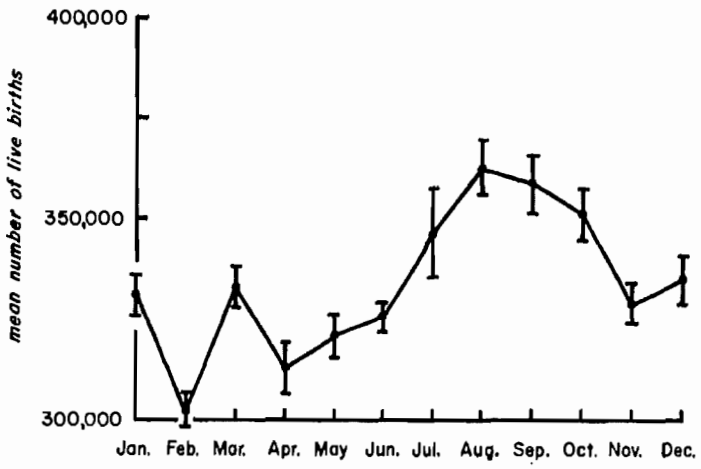


FIG. 8. Average live births, U. S. A., 1952–1967.

Clearly, the young infant population at risk was much greater during the summer months than in the winter and this was probably the most significant factor accounting for the increase in summer mortality. For every year of the period the live births showed a very marked increase between June and July and there was a further increase in the numbers in August (Table VII). The mean deaths, the mean live births and the number of deaths due to these diseases per 100,000 live births are shown together in Fig. 9. The numbers of infant deaths per 100,000 live births were greater during the months of May, June and July and the maximum number of deaths occurred in July, whereas the largest number of live births was on average in August. It is thus reasonable to postulate that some of these deaths may have been precipitated by excessive seasonal warmth. When the mean infant deaths are divided by the mean total deaths from all causes for the period 1952–1967, the resultant proportional mortality rates for June, July, August and September are greater than for any other month. This would, in part, be due to the fact that the numbers of deaths from all causes, the denominators, were less during these months than in any other month. When the mean infant deaths per 100,000 live births are divided by the mean deaths from all causes, the resultant ratios are, however, appreciably greater during May, June, and July which suggests that on average during this 16-year period a higher proportion of infant versus adult deaths occurred during these months than in any other month. Scrutiny of the heat deaths by age suggests that infants are more heat illness-prone than other age groups; but the rates per 100,000 in the Table in the Addendum at the end of this paper indicates that whereas infants are the most heat illness-prone group below 50 years of age, above 50 years adults are more heat illness-prone than infants and become progressively so as they grow older. Substantial clinical support that infants are more at risk than other patients is provided by Cardullo (1949) and Kessler and Andersen (1951).

MATERNAL MORTALITY

The General Mortality Tables were examined to see if maternal deaths increased in July or August. "Deliveries and complications of pregnancy, child-

TABLE VII

LIVE BIRTHS BY YEAR AND BY MONTHS: UNITED STATES—1952–1967

	Total	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.
1952	3,846,986	311,626	300,218	317,718	292,028	300,366	311,340	345,452	350,476	343,682	336,136	315,148	323,336
1953	3,902,120	322,488	296,312	315,132	286,962	307,382	321,246	354,464	356,450	347,740	334,202	319,966	339,776
1954	4,017,362	331,570	302,318	323,668	365,006	318,444	327,003	358,920	363,278	358,568	351,858	335,140	341,584
1955	4,047,295	328,872	306,418	332,407	309,198	325,859	324,847	254,267	367,221	361,973	354,304	336,565	345,364
1956	4,163,090	339,074	324,828	344,912	308,530	315,230	333,672	370,390	383,084	374,728	369,734	343,658	355,250
1957	4,254,784	346,462	317,380	348,378	331,212	344,740	348,054	380,020	381,448	377,002	376,254	348,158	355,676
1958	4,203,812	344,236	310,968	347,378	326,178	342,518	338,316	360,960	367,878	378,118	373,820	346,600	357,842
1959	4,244,796	349,334	322,706	358,192	331,144	337,614	342,814	373,766	380,078	377,220	368,198	345,688	358,042
1960	4,257,850	345,376	329,642	349,918	327,202	333,120	332,728	374,214	392,230	387,350	370,552	349,854	365,614
1961	4,268,326	353,286	327,502	360,322	335,120	342,404	341,990	373,522	385,484	377,628	370,114	346,556	354,398
1962	4,167,362	344,014	318,090	350,762	327,926	335,230	328,098	363,018	379,122	369,002	363,524	338,796	349,780
1963	4,098,020	339,188	310,846	340,494	322,936	334,238	331,952	360,454	367,290	365,002	356,866	328,732	339,996
1964	4,027,490	332,210	318,554	332,388	313,338	327,064	332,568	358,096	354,932	355,604	348,232	323,578	330,926
1965	3,760,358	312,668	288,238	317,394	293,254	306,732	308,234	332,838	336,754	333,620	320,556	301,864	308,206
1966	3,606,274	293,850	273,902	303,420	286,914	292,824	292,526	310,550	321,304	319,234	312,942	296,498	302,350
1967	3,520,959	293,056	268,664	296,915	270,618	290,600	289,953	309,569	313,276	308,535	303,305	284,192	292,274
Mean	4024180.	330456.	307286.	333678.	314222.	322147.	325333.	348781.	362519.	358437.	350662.	328812.	338775.
SD	236353.	18904.	18240.	19484.	23870.	18069.	16993.	32896.	22914.	22663.	22970.	20342.	21839.
SE	59088.	4726.	4560.	4871.	5967.	4517.	4248.	8224.	5728.	5665.	5742.	5085.	5459.

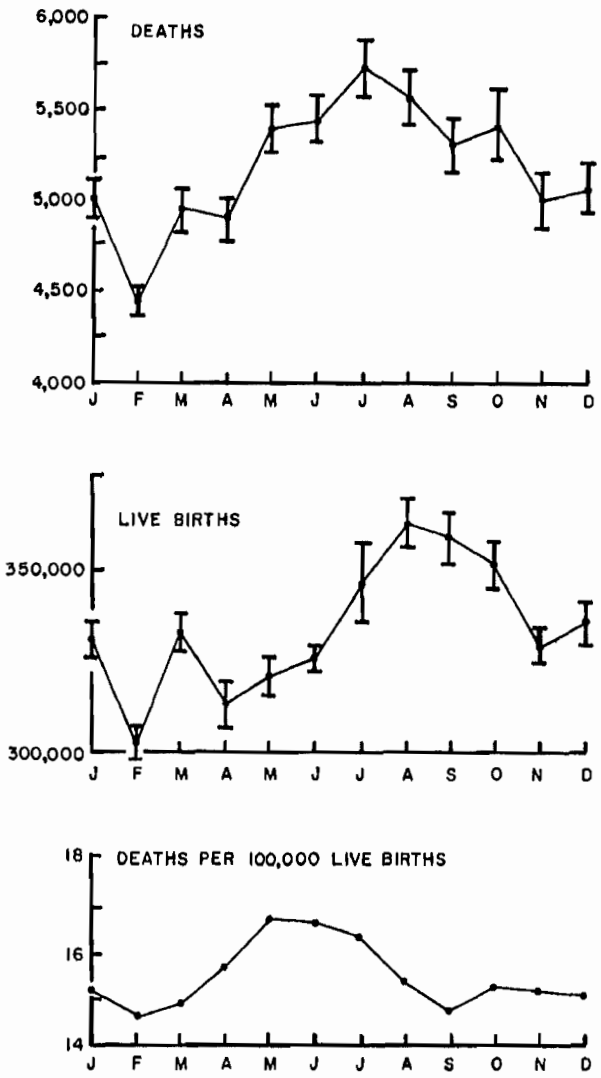


FIG. 9. Early infancy, U. S. A., 1952–1967.

birth and the puerperium" (640, 641, 681, 682 and 684) did show a small excess of deaths during July in some years but not all. The monthly numbers were very small, frequently not even running into 3 figures and rarely exceeding 150. These rubrics would, therefore, have had a negligible effect on the numbers of deaths from all causes each month.

SENILITY

There is no similar large category to that for infant deaths in the General Mortality Tables to cover diseases of the very old. The relatively small category "senility without mention of psychosis (ICD 794)" was therefore selected as an indicator disease. Figure 10 shows that on average there was a small increase in

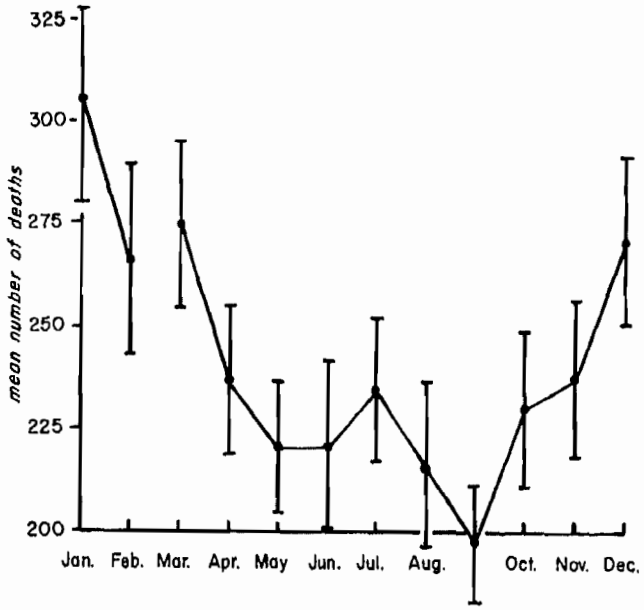


FIG. 10. Deaths from "senility without mention of psychosis," U. S. A., 1952–1967.

the numbers of deaths during July. Table VIII indicates that the maximum number of summer deaths occurred in June in some years but more frequently in July. When the mean numbers of deaths from senility are divided by the mean numbers of deaths from all causes the proportional mortality rate for senility is higher in July than in any other month except December. There is great variation between states in allowing certification to this "miscellaneous" category. Mississippi allows more than 5 times the proportion of most other states.

CARDIOVASCULAR DISEASE

It has been established that deaths due to cardiovascular diseases, particularly ischaemic heart disease, are more numerous during the winter than during the summer months (Rose, 1966; Boyd, 1960; Rosenwaike, 1966). In a 3-year analysis relating causes of death to the daily average temperature on the day of death for Memphis, Tennessee, Rogot and Blackwelder (1970) found that the average number of deaths from arteriosclerotic heart disease was highest (3.56) when the average temperature was below 30°F (−1.1°) and that the number declined steadily to a low of 2.12 for days when the average temperature was between 80°F (26.7°) and 90°F (32.2°). A similar relationship held for other groups of cardiovascular disease but not for deaths from cancer which were not affected by changes in air temperature. Cardiac deaths in which respiratory disease was present also showed an inverse relationship of temperature to cardiovascular mortality except for an increase in mortality on the hottest days. Heyer, Teng and Barris (1952) reported an increase in the numbers of deaths from acute myocardial infarction during the summer months for Dallas, Texas; and

TABLE VIII

DEATHS FROM "SENILITY WITHOUT MENTION OF PSYCHOSIS (794)" FOR THE UNITED STATES, BOTH SEXES, ALL RACES, BY MONTH: 1952–1967

Year	Jan.–Dec. (incl.)	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.
1952	4,790	434	423	504	382	363	**402**	**402**	344	304	410	367	455
1953	6,626	547	490	400	348	354	389	315	**369**	329	311	368	406
1954	3,829	425	347	325	322	273	**320**	**368**	289	243	273	322	322
1955	3,461	341	325	332	282	250	246	**297**	237	229	281	306	335
1956	3,131	343	282	291	255	245	232	239	231	214	225	240	334
1957	3,243	287	252	264	273	249	259	**265**	**252**	211	333	295	303
1958	3,000	344	291	289	254	261	170	**226**	**215**	205	218	228	299
1959	2,628	275	212	255	213	205	213	206	179	181	206	246	237
1960	2,639	308	260	278	203	190	**222**	182	166	163	222	196	249
1961	2,424	248	223	219	209	196	173	**185**	174	172	200	191	234
1962	2,426	287	218	221	177	193	173	**196**	**199**	154	184	214	210
1963	2,441	240	224	295	204	177	175	**181**	**188**	164	177	183	233
1964	2,234	233	223	187	189	162	152	**198**	156	166	176	187	205
1965	2,188	210	201	206	193	163	164	**183**	169	142	173	180	204
1966	1,958	215	181	188	175	144	141	**160**	**163**	122	152	153	164
1967	1,747	162	125	159	138	139	130	**153**	144	135	146	145	171
Mean	3047.	306.	267.	275.	238.	222.	222.	**234.**	217.	195.	230.	238.	272.

DePasquale and Burch (1961) reported similar findings from New Orleans for the years 1952–1955, when August was the month when there were most hospital admission of patients with coronary occlusion as well as the month with the highest death rate from this cause.

The General Mortality Tables were therefore examined to see whether the numbers of deaths from cardiovascular disease also showed an increase in the months when there was a high incidence of heat deaths. There were more deaths from arteriosclerotic heart disease, including coronary disease (420), in July 1955 and 1966 than in June or August. There was no adverse summer seasonal effect on mortality in 1952, 1953 and 1954. The numbers of deaths from other diseases of the heart (430–434) conformed with the normal seasonal pattern in 1952 and 1953 but in May 1954 and July 1955 and 1966 there were more deaths than in the preceding and following months. There was an increase in deaths from hypertensive heart disease (440–443) in one of the summer months in each of the years when there were more than 300 heat deaths. The average excess of deaths over the number of deaths in the months preceding and following was 733 in July 1955, 512 in July 1966, 493 in June 1952, 189 in May 1953 and 135 in May 1954. The significance of these figures is enhanced by the fact that in 10 of the 11 years when there were less than 300 heat deaths per annum there was no increase in mortality from hypertension during any of the summer months. In the 11th year, 1960, there was an average excess of 287 deaths in May.

Respiratory Disease

There were no excess deaths from diseases of the respiratory system during the summer in 1952, 1953, 1954 and 1955 but there was in July 1966.

Renal Disease

Gover (1938) included nephritis among the pathological conditions which accounted for excess deaths during the heat waves in Kansas and Illinois in 1934 and 1936 and 7 of the cases reported by Austin and Berry (1956) suffered with concurrent renal disease. Schrier, Henderson, Tisher and Tannen (1967) reported 8 cases of nephropathy associated with heat stress and exercise in the United States Army.

Urinary abnormalities and raised blood urea values were found by Shibolet *et al.* (1967) in all their severe cases of heat stroke in 36 young men. Other observers, notably Gauss and Meyer (1917), Ferris *et al.* (1938), Malamud *et al.* (1946), Ferguson and O'Brien (1960) and Barry and King (1962), also noted nonspecific urinary abnormalities in heat stroke patients such as mild azotemia, proteinuria, pyuria and hematuria. It would thus not have been surprising to find that the number of deaths from diseases of the genitourinary system increased during heat waves as a direct result of heat stress aggravating the underlying renal disease. Excess deaths from diseases of the genitourinary system were, however, not usually discernible during the summer months in the General Mortality Tables even during those months when there were a relatively large number of heat deaths during the 5 heat-wave years.

Diseases of the Blood and Blood-forming Organs

Halden, Jones, Sutherland and Muirhead (1955) reported the association of anemia with heat stroke and Wright, Reppert and Cuttino (1946) had earlier described the purpuric manifestations and hemorrhagic sequelae which frequently appear in the terminal stages of heat illness. Shibolet, Fisher, Gilat, Bank and Heller (1962) reported afibrinogenemia in 3 heat-stroke cases and later Shibolet, Coll, Gilat and Sohar (1967) found disturbances of the clotting mechanism with low prothrombin values in all their more serious cases. The average number of deaths from 1952–1967 from diseases of the blood and blood-forming organs, which includes the anemias (290–293), purpura and other hemorrhagic conditions (296) and all other diseases of the blood and blood-forming organs, comprising polycythemia (294), hemophilia (295), agranulocytosis (297), diseases of the spleen (298) and other diseases (299), did not show evidence of an appreciable summer increase in mortality. In June in 1952, 1954 and 1955 the month the heat waves started, there were on average 427 deaths from this group of diseases in contrast with 400 in May and 390 in July, while in 1966, the year with the greatest excess of deaths from all causes in July, there were 469 deaths in July as contrasted with 396 in June and 430 in August. Thus, deaths from diseases of the blood and blood-forming organs did increase in number during the summer months when heat deaths were numerous.

Homicides and Suicides

Schuman (1967) noticed that homicide contributed to the excess numbers of deaths in New York City in July 1966. Examination of the figures for the United States for 1952–1967 showed that on average there were 723 deaths from homicide in June, 828 in July, 822 in August and 770 in September. The average June–July excess of 105 deaths is a larger number than would be expected because there were 3% more days available in July than in June, nor could the excess number of deaths in August over those for September be explained in full because there are only 30 days in September. The figures for the heat-death years were similar and in 1966 there were 300 more homicides in July than in June. Whether or not these aggravated homicidal tendencies could be attributed to excessive seasonal warmth or to other sociological factors associated with the vacation season remains an open question but the figures for 1966 are suggestive. Additional weight is given to the conclusion that there may be a seasonal effect where the homicidal psychopath is concerned but not in the case of the depressive by the fact that in only 2 of these 16 years, August 1962 and July 1965, neither of which were heat-wave years, was there any suggestion of a summer excess of deaths due to suicide.

Alcoholism

The observation that homicidal deaths increased during the warm summer months prompted the scrutiny of deaths from alcoholism (ICD 322). The average numbers each month for this 16-year period were May 181, June 185, July 195, August 176. Even when allowance is made for the 3% difference in the num-

TABLE IX

MORTALITY FROM EXCESSIVE HEAT AND INSOLATION (E931), NO. DEATHS, TOTAL, BY RACE, BY SEX: UNITED STATES: 1952–1967

Year	Total	White		Nonwhite	
		Male	Female	Male	Female
1952	1,401	743	371	185	102
1953	576	319	142	85	30
1954	978	518	286	102	72
1955	615	393	139	61	22
1956	174	99	39	22	14
1957	280	157	65	46	12
1958	137	84	19	26	8
1959	267	137	57	48	25
1960	168	101	33	25	9
1961	191	108	53	19	11
1962	154	177	27	42	6
1963	196	109	32	34	11
1964	195	112	46	29	8
1965	106	48	19	31	8
1966	531	212	163	79	77
1967	96	64	14	15	3
Total	6,065	3,381	1,505	849	418
Mean	379	211	94	53	26
SD	364	191	103	43	30
SE	91	47	25	10	7

ber of days in June and July there were more deaths from alcoholism in July than in any other of the summer months. In 1966 there were 246 deaths in May, 255 in June, 292 in July, 238 in August and 197 in September. The number of deaths from alcoholic psychosis (ICD 291) showed a similar trend in some years

TABLE X

DEATHS FROM EXCESSIVE HEAT AND INSOLATION (E931), BY AGE, FOR THE UNITED STATES, 1952–1967 FOR YEARS WHEN THE TOTAL HEAT DEATHS WERE IN EXCESS OF 300 PER ANNUM

Age and Year	Total	Under 1 year	Under 5 years	5–19 years	20–34 years	35–49 years	50–64 years	65–79 years	80–94 years	Over 95	Not stated
1952	1,401	71	96	21	93	240	350	380	207	11	3
1953	576	22	31	18	48	96	171	131	72	4	5
1954	978	57	70	7	47	127	195	288	231	10	3
1955	615	21	28	6	25	117	173	173	85	5	3
1966	531	12	19	12	21	73	131	162	106	7	—
Mean	820.	36.	40.	12.	46.	120.	204.	226.	140.	7.	2.8
SD	370.	25.	32.	6.	28.	64.	84.	104.	73.	3.	1.7
SE	165.	11.	14.	2.9	12.	28.	37.	46.	32.	1.9	.8
Total	4,101	183	244	64	234	653	1,020	1,134	701	37	14

TABLE XI
MORTALITY FROM EXCESSIVE HEAT AND INSOLATION IN MISSOURI, TEXAS, CALIFORNIA, AND ILLINOIS—1952–1967

Year	Missouri	Texas	California	Illinois
1952	195	55	40	78
1953	71	41	28	24
1954	235	95	27	58
1955	72	17	47	76
1956	13	21	11	8
1957	20	29	16	11
1958	5	25	15	2
1959	8	28	21	14
1960	17	20	34	8
1961	10	10	61	10
1962	5	41	16	1
1963	9	26	22	4
1964	12	29	11	15
1965	5	19	15	4
1966	186	8	18	70
1967	0	5	22	3
Total	863	469	399	386

but the numbers were only about one-third of those for alcoholism and are inconclusive.

In Tables IX–XIII the distribution of deaths from excessive heat and insolation are shown for 1952–1967 by race, by sex, by year, by age and by state.

RACE AND SEX

The numbers of deaths in the United States for white and nonwhite persons and for both sexes are tabulated in Table IX which indicates what a random business it is to guess ahead at the likelihood of heat waves occurring. The 4

TABLE XII
MEAN DEATH RATES PER ANNUM FROM EXCESSIVE HEAT AND INSOLATION; BY STATE, 1952–1955

Rate/100,000	States
>4.0	Missouri
3.0–3.9	—
2.0–2.9	Kansas, District of Columbia, Oklahoma
1.0–1.9	Iowa, Nebraska, Arizona
0.5–0.9	New Jersey, Indiana, Illinois, Maryland, Delaware, South Carolina, Georgia, Kentucky, Tennessee, Arkansas, Texas
0.1–0.49	New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Ohio, Pennsylvania, Michigan, Wisconsin, Minnesota, North Dakota, South Dakota, Virginia, West Virginia, North Carolina, Florida, Alabama, Mississippi, Louisiana, Montana, Wyoming, New Mexico, Nevada, Washington, California
<0.1	Maine, Oregon, Idaho, Colorado, Utah

TABLE XIII

MEAN DEATH RATES[a] FROM HEAT AND INSOLATION PER 100,000 FOR 1952–1955 AND DEATH RATES PER 100,000 FOR 1966, BY STATES AND REGIONAL DIVISIONS

States and Divisions	1952–1955	1966
Maine	0.09	0
New Hampshire	0.14	0
Vermont	0.13	0
Massachusetts	0.17	0
Rhode Island	0.18	0
Connecticut	0.14	0.06
New England	0.14	0.01
New York	0.27	0.19
New Jersey	0.82	0.13
Pennsylvania	0.45	0.13
Middle Atlantic	0.5	0.15
Ohio	0.33	0.10
Indiana	0.54	0.26
Illinois	0.64	0.65
Michigan	0.24	0.02
Wisconsin	0.1	0.19
East North Central	0.37	0.24
Minnesota	0.27	0.27
Iowa	1.24	0.50
Missouri	4.15	4.10
North Dakota	0.13	0.10
South Dakota	0.31	0.15
Nebraska	1.27	0.69
Kansas	2.10	0.40
West North Central	1.35	0.89
Delaware	0.64	0.20
Maryland	0.74	0.03
District of Columbia	2.0	0.12
West Virginia	0.25	0.06
Virginia	0.43	0.09
North Carolina	0.49	0.02
South Carolina	0.57	0.12
Georgia	0.76	0.04
Florida	0.18	0.12
South Atlantic	0.67	0.09
Kentucky	0.61	0.19
Tennessee	0.54	0.52
Alabama	0.46	0.23
Mississippi	0.37	0.21
East South Central	0.50	0.29
Arkansas	0.82	0.77
Louisiana	0.22	0.08
Oklahoma	2.50	0.16
Texas	0.61	0.17
West South Central	1.04	0.30
Montana	0.20	0
Idaho	0.08	0
Wyoming	0.10	0.30
Colorado	0.09	0
New Mexico	0.20	0.10
Arizona	1.3	0.87
Utah	0.07	0.20
Nevada	0.24	0.22
Mountain	0.29	0.21
Washington	0.1	0.03
Oregon	0.08	0
California	0.32	0.10
Alaska	—	—
Hawaii	—	—
Pacific	0.33[b]	0.04[b]

[a] For total resident population in the United States on 1st July, including the Armed Forces.
[b] Excluding Alaska and Hawaii.

years 1952–1955 were all "heat-wave" years, when more than 500 heat deaths were reported and there were no more severe heat waves until 1966. With the exception of 1957 and 1959 there were less than 200 deaths in each of the other 11 years.

There were always more deaths of whites than nonwhites and male deaths, whether white or nonwhite, were more numerous than female deaths in every year. However, as there were approximately 7 times as many white persons as nonwhite the incidence of nonwhite heat deaths was, in fact, about twice that for both sexes in the white population.

Age

The distribution of heat deaths in the United States by age is shown in Table X for the 5 years 1952–1955 and 1966. In persons aged 65 years or older 1,886 deaths occurred; 1,020 were deaths of persons between 50 and 65 years of age; 653 deaths were of persons 35–49 years of age; there were only 234 deaths between 20–34 and only 64 between 5–19 years of age; the healthiest age group of all in this respect. The large number of deaths in the under-5-year age group indicates that this was the most vulnerable age group under 50 years of age, deaths of infants under 1 year of age contributing 183/244 of the deaths. On this evidence, infants must be considered one of the more heat illness-prone age groups and the heat-death rates per 100,000 for the 5 heat-wave years in the Addendum confirm that this is so below 50 years of age but not after 50 years.

State

Some indication of the sporadic occurrence of deaths from excessive heat and insolation is given in Table XI. Between 1952 and 1967 there were more deaths in Missouri, Texas, California and Illinois than in any other state but 616 of the 863 heat deaths which were reported in Missouri occurred in only 3 years—1952, 1954 and 1966—and the figures for the other 13 years compared favorably with the figures for Texas or California more often than not. The pattern for Illinois was similar to that for Missouri, although the numbers were smaller. On the other hand, the death rates per 100,000, calculated from Population Estimates, Series P25, for 4 years when more than 500 deaths were certified to be due to heat per annum and summarized in Table XII, places Texas, with a rate of 0.62 per 100/000, with a lower rate than not only Missouri but also Kansas, the District of Columbia, Oklahoma, Iowa, Nebraska, Arizona, Arkansas, Georgia, Maryland, Illinois and New Jersey, while California is 24th in line.

The average regional distribution of heat deaths during the heat-wave years in the early 1950s in Table XIII indicates the widespread character of these heat waves and the death rates for 1966 show that, as far as this criterion was concerned, the effects of heat were more serious in the early 1950s than in 1966 in every region.

Temperatures During Heat Waves

The Weather Bureau Monthly Reviews for 1952–1955 and 1966 confirm that these were years when it was unusually hot in many parts of the country. The

first week of May 1952 was predominantly warm in the Central Plains being as much as 15°F (8.4°) above normal but lower temperatures were recorded later so that the average for the month was 4°F (2.2°) below the normal average. It was possible that some early acclimatization occurred and more deaths from heat were coded in May than in April. June was the hottest June on record in more than a dozen cities with the most extensive and prolonged heat wave in recent years in the eastern two-thirds of the United States. The greatest anomaly was an excess of 10°F (5.6°) mean monthly temperature in Kansas City, Missouri. In Nashville, Tennessee a mean monthly temperature of 85°F (29.4°) was 3°F (1.6°) higher than the monthly average and higher by 2°F (1.12°) than for any month in history, the temperatures being 100°F (37.8°) or above for the last 8 days and more than 90°F (32.2°) for the last 28 days. Temperatures in excess of 100°F (37.8°) were recorded as far north as Detroit and Boston and on 27 June, Washington, D. C. had the hottest night in 80 years, a minimum temperature of 82°F (27.8°) being recorded after a maximum of 101°F (38.3°) on the previous afternoon. Temperatures well above normal continued during July; daily maxima ranging up to 112°F (44.4°) in South Dakota, 110° (43.3°) in Georgia, 109°F (42.8°) in Kansas, more than 100°F (37.8°) for 9 successive days in Chattanooga and in New York City 14–23 July was the warmest 10-day stretch on record. Similar severe heat continued throughout July but ended in early August with a series of cold fronts, to be followed by abnormally warm weather east of the Rockies in the first half of September and in the Far West in the latter half of the month; while October was the dryest month ever observed over the United States as a whole with abnormally high temperatures from the Rockies to the Pacific Coast with little relief until after the first week in November.

During the summer of 1953 cool spells alternated with intense heat waves, usually of relatively brief duration. May was rather warmer and more humid than usual with sharp swings in temperature over short periods so that, although the average was close to normal, some extreme temperatures occurred; thus, in Oklahoma and northwest Texas during the week ending 18 May the temperature was 12–13°F (6.7–6.8°) below normal but a week later the average temperature was 9–11°F (3.9–6.1°) above normal in the same area and record maximum temperatures for the time of year occurred at several stations, 102°F (38.9°) being reported at Amarillo, Texas on the 25th. Extremely dry weather prevailed over the lower Mississippi Valley, Southern Great Plains and the Southwest in June and was accompanied by a prolonged and severe heat wave except in Southern California and Arizona. Maximum temperatures in the 90s or over occurred in most of the drought area and at Abilene, Texas there were 21 days with maximum temperatures in excess of 100°F (37.8°) which set a new record for June, while at many other stations in Texas, Oklahoma, Kansas, New Mexico, Louisiana, Arkansas and Tennessee monthly mean temperatures were the highest on record for June. At Memphis, Tennessee and Lake Charles, Louisiana June 1953 was not only the warmest June on record but also the hottest month ever observed. Early July saw intensification of the heat in the Southwest but after the first 10 days conditions were cooler and the drought was relieved. There was a further prolonged dry spell when toward the end of August tem-

peratures again rose to record-breaking levels, first in the Northern Plains and then progressively eastward and southward, the heat being particularly intense between 30 August and 3 September, examples of high temperatures being 107°F (41.7°) at Hagerstown, Maryland; 106°F (41.1°) at Fredericksburg, Virginia; 105°F (40.6°) at Newark, New Jersey; 103°F (39.4°) at Louisville, Kentucky and Huntingdon, West Virginia; 102°F (38.9°) in New York City and at Evansville, Indiana, Cincinnati, Ohio, Pine River, Wisconsin and Baltimore, Maryland, and 101°F (38.3°) at Chicago, Illinois, Cleveland, Ohio, Philadelphia, Pennsylvania, St. Louis, Missouri and Hartford, Connecticut. The heat wave was unusual not only for its intensity but for its duration and extent. There were 12 straight days in Washington, D. C. with temperatures above 90°F (32.2°) and 7 days in a row with temperatures above 95°F (35°) between 26 August and 5 September, while Richmond, Virginia had 5 consecutive days with maxima of 100°F (37.8°) or more, starting on 29 August. Another record-breaking heat wave occurred in the last weeks of September with temperatures soaring to 105°F (40.6°) in Concordia, Kansas and Fort Worth, Texas on the 28th and 102°F (38.9°) in St. Louis, Missouri the next day. This was the 5th consecutive month with a heat wave in the last week of the month in a large portion of the eastern states. Early October was warmer than usual with temperatures rising to 101°F (38.3°) at Los Angeles and Burbank, California, with a record of 95°F (35°) at Bismarck, North Dakota, ending one of the hottest summers of all time. The temperature pattern was reflected by the numbers of heat deaths coded in May and September which were greater than in any other May or September of the 5 heat-wave years. An excess number of deaths from all causes over the number of deaths in the month preceding or following the heat-wave months were not apparent during any of the summer months because they were all heat-wave months but the number of deaths from all causes were appreciably higher in June, August and September 1953 than in the corresponding months in 1952 and 1954.

May 1954 was a cooler month than usual but heat and drought dominated the eastern two-thirds of the Nation for the 3rd consecutive June, except for the northern tier of states, commencing in the Mississippi–Ohio Valley. The greater portion of the central states remained warmer than usual in July. Heat and drought were particularly severe in the 6 state area—Nebraska, Kansas, Oklahoma, Louisiana, Missouri and Arkansas. Above normal temperatures were persistent and extreme temperatures of 115°F (46.1°) were recorded at St. Louis on the 14th and 117°F (47.2°) at East St. Louis on the 17th. The average monthly temperature ranged from 6°F (3.3°) to 8°F (4.4°) above normal levels in South Dakota, Tennessee, Texas, Southeast Kansas, Northeast Oklahoma and adjacent areas of Kansas, Missouri and Arkansas. At Wichita, Kansas, maximum temperatures of 100°F (37.8°) or over were recorded for 20 days, the average maximum temperature being 103°F (39.4°) with an extreme of 113°F (45°). The mean monthly temperature of 89.3°F (31.9°) was 8.4°F (4.5°) above normal and made this the hottest month on record. The hot weather continued into August, when temperatures were above normal from the Rocky Mountains to the Atlantic Coast, and into September when there were unusually high tem-

peratures during the 1st week, 103°F (39.4°) being recorded in Kansas City, Missouri, 104°F (40°) at St. Louis, Missouri and 105°F (40.6°) at Nashville, Tennessee.

A cool May and June in 1955 was followed by one of the longest and most prolonged heat waves ever observed in July which covered the United States from the Continental Divide to the Atlantic Coast except for the Gulf Coast. The hottest weather occurred during the last week and centered in Iowa where temperatures 12°F (6.7°) above normal were observed for the entire period, with 100°F (37.8°) or more for the last 5 days at Des Moines and a high of 105°F (40.6°) on the 31st. Omaha, Nebraska had its hottest day at this time with 108°F (42.2°). No absolute maximum temperature records were broken, although many cities reported their highest July monthly average temperature on record, including Chicago, Cleveland, Detroit, Hartford, New York, Newark, Philadelphia, Baltimore and Washington, D. C. Cities, where the persisting temperature above 90°F (37.8°) broke or equalled all records, in addition to the above, were Minneapolis, Lansing, Indianapolis, Albany and Boston. New Jersey experienced the hottest July since 1888. The intense heat continued through August across the northern half of the country east of the Rockies into September when the heat wave was still intense in the West, temperatures ranging up to 110°F (43.3°) in Los Angeles, 111°F (43.9°) at Red Bluff, California and 107°F (41.7°) at Medford, Oregon with many new records being established at different weather stations. There were 8 successive days at Los Angeles from 31 August with readings which exceeded 100°F (37.8°) and constituted a record for this month. Toward the latter half of September the weather moderated but temperatures in excess of 100°F (37.8°) were still recorded in central parts of the country where Jackson, Missouri experienced the highest temperature of the year, 97°F (36.1°) on 27 September. October adhered to the usual monthly weather except for New England where there was a record high temperature of 82°F (27.8°) at Boston, Massachusetts on the 11th which was followed by frost on the 23rd.

May 1966 was warm and dry in the West, the highest temperatures being 6.8°F (3.8°) above normal in Nevada. The heat wave began toward the end of June in the northern Mississippi Valley and the Northeast and intensified in July, spreading south and southwest. Reports from 42 major weather stations from the Rocky Mountains to the Atlantic Coast indicated record high temperatures during the month. Between the 10th and the 16th an average of 370,000 square miles in the eastern two-thirds of the nation had temperatures which exceeded 100°F (37.8°) and on the 11th approximately 527,000 square miles were exposed to similar temperatures. August 1966 was unusually cold and so was September, except in the West, where the largest departure from normal in western Montana was 6°F (3.4°). This was a brief but severe heat wave occurring after several years of milder summer weather.

DISCUSSION

This review was discussed at a Workshop of epidemiologists, biometrists and meteorologists convened by the National Institute of Environmental Health

Sciences, North Carolina, on 28 and 29 April 1971 and has been amended in the light of comments made at that time and subsequently.

Certification and Coding

The certification and coding of deaths due to heat is unsatisfactory. The World Health Organization's Sixth Decennial International Revision Conference for the International Classification of Diseases agreed in 1948 that the cause of death to be tabulated should be the *underlying* cause defined as "(a) disease or injury which initiated the train of events leading directly to death—or, (b) the circumstances of the accident or violence which produced the fatal injury." Doctors also avoid certifying a cause of death which might lead to a time-consuming coroner's inquiry, liability for compensation or damages, criticism by authority or a military command, family distress and for other reasons, for heat illness in a healthy community in peace time is nearly always a preventable condition. It should not occur. Certification habits vary from state to state and from time to time. If there have been a succession of heat-illness epidemics in recent years or months, the medical profession becomes heat-illness conscious. If there has not, the diagnosis, especially the secondary diagnosis, is more likely to be missed or omitted. Thus, the numbers of deaths from excessive heat and insolation in the General Mortality Tables understate the true mortality from heat disorders by a considerable, but unknown, margin and many deaths primarily caused by excessive heat and deaths aggravated or precipitated by excessive heat are absorbed into the deaths from all causes under one rubric or another.

In order to clarify some of the misunderstandings in relation to the period under review the basic coding rules which were applied from 1952–1967 were summarized by Dr. Moriyama, Director, Office of Health Statistics Analysis as follows:

> "For data years 1952–1967, the international rules for classifying causes of death were applied when effects of heat such as heat stroke, sunstroke and heat apoplexy were reported as causes of death. In some instances where one of these effects of heat was jointly reported with organic diseases, the application of the international rules did result in assignment to the organic disease. In other instances, however, the rules resulted in assignment to effects of heat.
>
> For data years 1952–1954, certifications which listed any effect of heat were coded in accordance with the international coding rules unless there was evidence that the listed condition was used to refer to some slightly abnormal weather or temperature condition. In 1952 and 1953 an investigation was undertaken to try to determine the relationship of certain effects of heat to other reported causes and to death. During this period, participating registration areas were asked to query all certifiers who reported effects of heat such as excessive heat, exposure to heat, heat exhaustion, effects of heat, heat cramps, heat fever, heat prostration and overheated as a cause of death. The results of this investigation indicated that in most instances the heat was an aggravating condition rather than the underlying cause of death. On this basis a change in coding procedure was made in the Center for deaths occurring in 1955. The effects of heat mentioned above were not coded as the underlying cause of death unless they were the only conditions reported. However, no changes were made in the coding rules issued by the World Health Organization.
>
> For data years 1956–1967, the effects of heat included in the study mentioned

above usually were not coded as the underlying cause of death if a condition not classifiable to the symptom and ill-defined categories was reported in Part I of the medical certification."

Dr. Moriyama's summary underlines the difficulties in assessing the relative effects of different heat waves only from counts of the numbers of heat deaths which were certified or coded. The practice varied from time to time and a more reliable indication of the true mortality due to heat will usually be provided by the number of deaths from all causes or from certain indicator diseases such as arteriosclerotic disease of the brain or the heart.

Even in 1966 coding procedures varied greatly from state to state and even for the same state. In St. Louis, e.g., in one of the more heat-conscious states, Missouri, only 130 deaths were coded as due to heat in July 1966 (Schuman, 1967) but, from their detailed review of death certificates for only part of this month, Henschel and his co-workers (1968) found excessive heat to be a primary cause of 259 deaths and a secondary cause of 40 other deaths, while the Vital Statistics Office General Mortality Tables show only 186 deaths due to excessive heat and insolation (E931) in the State of Missouri for the entire year of 1966.

Deaths from All Causes

July is 3% longer than June (and February has 10% fewer days than the 31-day months which accounts for the February dip in Figs. 3, 4, 7–10). When this is taken into consideration, with the facts that it is also the start of the vacation season and the month when there is a great increase in live births every year, and thus in the infant population at risk, a substantial nonclimatic explanation is offered for many of the excess deaths in July and also for the humps in the average seasonal mortality curves of Rosenwaike and Kutschenreuter. In years when a large number of heat deaths were concentrated in 1 or 2 summer months, such as in 1952 or 1966, the large number of excess deaths from all causes in the month or months when there were most heat deaths are, however, almost certainly largely due to heat-aggravated or heat-precipitated illness.

The available vital statistics do not suggest that there was a very great mortality from heat-aggravated or heat-precipitated illness in years when there was not a heat wave. Furthermore, when the heat wave was of gradual onset, as shown by the gradual increase of heat deaths throughout the summer months in 1953, the numbers do not suggest that there was a very appreciable excess of deaths from all causes. Although it is likely that some deaths precipitated by excessive environmental warmth were submerged in the deaths from all causes in most of the months when appreciable numbers of heat deaths were recorded.

The vital statistics alone do not support the contention of the United States Public Health Service Joint Task Force (1970) that "every year thousands of people die and many more suffer from thermal exposure in the United States." This conclusion should, however, be tested by more careful prospective studies of mortality and morbidity in areas where acute heat illness has been found to be endemic over the years. Prospective studies in large cities rather than states would probably be more informative, especially in large states where climatological conditions vary considerably and dilute the heat-illness data in areas where

heat waves are most severe. Some light might also be thrown on the incidence of morbidity due to heat by the examination of case notes on discharge from large hospitals in areas where heat illness is known to be endemic.

The truth probably lies somewhere between the alarming conclusion of the Task Force and the less alarming, but nevertheless disturbing, story told to date by the General Mortality Tables. When relatively large numbers of deaths are tabulated as due to heat and are concentrated in 1 or 2 months, the excess deaths, which include deaths due to heat-aggravated or heat-precipitated illness, very greatly outnumber the deaths coded to be due to heat alone. The average number of deaths from "all causes" for the 4 years—1952, 1954, 1955 and 1966—was 7,225 less for the months preceding the heat-wave months than the average for the heat-wave months and 10,013 less for the months following the heat-wave months. There were thus, on average, 8,619 excess deaths from all causes in these heat-wave months. The corresponding average number of heat-certified deaths for these 4 years was 579. The average excess numbers of deaths from all causes in the heat-wave months was then at a conservative estimate in the region of 6,000, even when allowance is made for July being a longer month than June, the July increase in live births and deaths from accidents with the start of the vacation season. Heat-aggravated illness or heat-precipitated illness thus accelerated the demise of at least 10 or 11 times as many persons as were certified to have died from the effects of heat during these heat waves.

Meteorological Data

Weather-station data require careful interpretation as well as vital statistics. Macpherson and his colleagues (1967) found that the maximum 3 PM shade temperature at the institution in the suburbs of Sydney where they collected their data on mortality was about 8°F (4.4°) higher than the temperature recorded at the city weather station near the harbour. It is likely that differences of the same order, or greater, occur between recordings made at airport weather stations and in other open areas and those which occur in the more congested parts of many American towns and cities. Current proposals to broaden the network of weather stations to cover the less satisfactory areas of cities more comprehensively should go some of the way to fill this gap. There is also a need for detailed 24-hour studies of the microenvironment in the actual areas where casualties occur during heat waves by skilled observers to identify the more sinister characteristics on the spot rather than by guessing at them in retrospect from second-hand data. The highest minimum temperature at night, which prevents recuperation during the hours of darkness, may be a more serious cause of heat stress than the highest daytime maximum and this may have been the case in New York City on 24 September, 1970.

Power Cuts

The repeated confirmation of Gover's (1938) observations that it is usually the first heat wave of the year which causes the greatest number of heat deaths even though later heat waves may be more severe and last longer and that most

deaths occur in the first few days of the first heat wave, coupled with the fact that this is the time when power cuts are most likely to jeopardize the efficient operation of air-conditioning equipment and many types of ventilating and circulating fans which rely on electrical power, poses a real threat of a disaster situation occurring with dramatic suddenness in states which today rely on air-conditioning more than hitherto if the development of power supplies has not kept pace with the increase in air-conditioned buildings.

Air Pollution

High levels of air pollution are associated frequently with excessive heat and humidity. One of the antipollution measures advocated in towns and cities is to reduce the fuel consumption of generating stations. Presumably this also reduces the power which is generated. It would indeed be droll if this increased the death rate from heat illness and heat-aggravated illness during heat waves, particularly in the air-conditioned community, by cutting the power supplies needed for effective air-conditioning and for ventilating and circulating fans to lethal levels. Clearly the priorities for remedial measures to combat high air pollution and excessive heat when they occur together must be considered in the full light of all the circumstances and call for careful judgment.

There is little doubt that at times the associated effects of excessive environmental warmth are played down or even ignored by those studying the effects of air pollution. In an otherwise comprehensive review, citing 73 references, Lave and Seskin (1970) do not refer to the possible associated effects of high levels of environmental warmth and conclude "a substantial abatement of air pollution would lead to a 10–15% reduction in the mortality and morbidity rates for heart disease." Although they admit "the evidence relating cardiovascular disease to air pollution is less comprehensive than that linking bronchitis and lung cancer to air pollution." On the evidence available this would seem to be a naïve, extravagant and optimistic claim. This is borne out by a recent report by Hexter and Goldsmith (1971) on the association between the total numbers of deaths occurring in Los Angeles County each day from 1 January 1962 to 31 December 1965 and the daily air temperatures and carbon monoxide and oxidant content of the air. Regression analysis showed that carbon monoxide levels were associated significantly with mortality but cyclic variation and maximum temperatures were much more important. There was no association between mortality and the level of oxidants in the air.

At the National Institute of Environmental Health Sciences' Workshop, Buechley (1971B) presented a spot map of the United States which showed the mortality ratios (to expected deaths) for counties making up the weather areas by day in 1966. The figures plotted on these maps showed no effect of recorded levels of air pollution on death rate but a marked effect of the recorded levels of heat on mortality, particularly in New York, Illinois and Missouri. Control of the thermal environment indoors should be accorded at least as high priority as control of air pollution when high air temperatures and high levels of air pollution occur simultaneously, if the preservation of human life is indeed the first consideration.

The 1966 Heat Wave

Certain features of the 1966 heat wave call for further comment. This was a less protracted heat wave than the heat waves in the early 1950s. More than 10 deaths were coded to be due to heat in only 11 states in 1966: Arizona, Arkansas, California, Illinois, Indiana, Iowa, Missouri, New York, Pennsylvania, Tennessee, and Texas but in 27 states in 1952: Alabama, Arizona, California, District of Columbia, Florida, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Mississippi, Missouri, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Virginia and West Virginia, when more than half the country was in the heat-wave area at one time or another. More than twice as many heat deaths occurred in 1952 as in 1966 but there were more than twice as many excess deaths from all causes in July 1966 as in June 1952, the months when most heat deaths occurred. The excess deaths from cerebrovascular accidents, arteriosclerosis, including coronary disease, respiratory disease and diseases of the blood and blood-forming organs were greater in July 1966 than in 1952. Thus mortality from heat-aggravated illness was greater in 1966 than in 1952 but mortality certified to be due to heat illness *per se* was very much less. Why should this be? Was it because of the suddenness with which the 1966 heat wave occurred in a population which had not been exposed to severe heat for 11 years, or was it because the increasing use of air-conditioning in the interim had created a less well acclimatized and therefore a more heat illness-prone community? Were there power cuts to aggravate the situation and put air-conditioning plants and ventilation fans out of action?

Long-term Acclimatization

Practically nothing is known about the effects of long-term acclimatization. Do people continue to become more resistant to high temperatures with repeated exposure over years as well as for weeks or months? Was the community to some extent afforded some protection against the heat in 1953, 1954 and 1955 because of its severe experience in 1952? Or was the lower mortality in these years simply due to the prior elimination of most of those members of the community who were most susceptible to heat stress in 1952? Were people less immune to heat in 1966 because there had not been a severe heat wave for 11 years?

Physiological acclimatization is only part of the story of adaptation to life under unduly warm conditions. Alterations in behavioural characteristics relating to clothes, habits, work routines, diet, alcoholic intake, the location, orientation or construction of dwellings and public buildings, the provision of adequate windows, ventilation, air-conditioning of whole houses or office blocks or of single rooms and the use of extractor and circulating fans all play a part in what has been glibly called "culturization" as opposed to acclimatization. The need for sociologic, economic and town-planning studies is probably as great as, if not greater than, the need for physiological studies. To give but one example, if the United Nations' building was rotated 90 degrees there would be a saving of

thousands of dollars a day in the cost of summer air-conditioning, although the building might be less attractive architecturally. The summer gain would not be offset by winter losses as sunshine is less powerful and less likely to penetrate the smog in winter in New York City (Lee, 1971).

A Sporadic Hazard

Perhaps the most serious aspect of this problem lies in the sporadic way with which heat waves strike in time and space. The 1952 heat wave was certainly the most severe episode during the past 20 years but equally severe or more severe heat waves than this have been reported, notably in 1934, 1936 and in 1901. Some indication of the effect of the 1934 heat wave on mortality may be obtained from the Bureau of the Census Vital Statistics Special Report for 1934. The numbers of heat deaths are not given but the total deaths by months are. These show that in July of that year in the United States there were 5,345 more deaths than in June and 12,302 more deaths than in August. There was an increase in deaths from all causes in 25 states, which was most striking in Missouri where there were 3,717 deaths in June with 5,237 in July and 3,711 in August.

The heat wave in 1901 started toward the end of June in the lower Missouri and middle Mississippi valleys, to extend to eastern Colorado, Kansas, the adjoining sectors of Nebraska and Oklahoma, the whole of Missouri, Arkansas, Illinois, western Kentucky and Tennessee, where daily maxima ranged from 95–100°F (35–37.8°) and it continued with scarcely a break until 27 July. There were only 11 registration states in 1901 and the following figures from a Special Report of the Census Office on Mortality, 1900–1904, throw some light on the catastrophic effect of this heat wave: 518,207 deaths were certified from these states alone, with 4,012 deaths due to excessive heat and sunstroke, whereas, in the following year only 508,640 deaths from all causes were certified and only 290 heat deaths.

Heat and Cardiovascular Disease

The more serious short-term effects of excessive heat and humidity are due to the direct impact on the body's thermoregulatory mechanism, water and electrolyte balance and the greatly increased demands which are made on the cardiovascular system by diversion of the blood from central organs to the periphery to augment heat loss and sweating. Burch and his co-workers in New Orleans have shown the alarming magnitude of these effects on the cardiovascular system, particularly when this system is failing (Burch and DePasquale, 1962; Burch and Miller, 1969; Burch and Giles, 1970) and Burch and Ansari (1968) have shown that patients with congestive heart disease do not acclimatize as well as normal controls. There is little doubt that the increased mortality from arteriosclerosis of the heart and brain and from other diseases of the heart during heat waves could be greatly reduced by adequate climate control and regulation of the activities of those known to be suffering from these disorders or of those in the age groups where the mortality from them is greatest.

Excessively warm weather may also increase morbidity or mortality from

hypertensive heart disease. In the Tecumseh (Michigan) Community Health Study (Schuman, 1962), those who admitted to having had heat stroke or sunstroke in the past were 5 times as prone to develop hypertensive disease later in life than those who had no previous history of heat illness. Added weight is given by the observation made here that there was a summer excess of deaths in the United States from hypertensive heart disease in either May, June or July in each of the heat-wave years, 1952–1955 and 1966, and the contrasting experience in the other 11 years for which information is available in only one of which did such an excess occur. These two isolated observations suggest the need for careful assessment of the possibly aggravating effects of climatic factors in intensifying the course of hypertensive disease and the associated need for special observation and guidance for patients in hypertension clinics in hot weather.

Infant Deaths

The requirements of infants call for very special attention and the gravity of the emergency for these young persons when a severe heat wave occurs may be underestimated, not only by the parents but also by the medical attendants (Danks, Webb and Allen, 1962). Although malnutrition, birth injuries, underdevelopment and congenital illness were predisposing factors in a majority of the heat-illness admissions reported by Danks and his colleagues, one-third were normal babies. During the past 20 years the average number of deaths from acute heat illness was greater for infants under 1 year of age than for any other age group below 50 year of age. The thermoregulatory control in infants is less stable than in adults and older children and the sweat losses in proportion to body weight are more than double those in adults. But, provided one is aware of the gravity of the emergency and knows what to do, heavy mortality should not occur. Little is known of the nature of acclimatization in infants and in small children.

The Aged

The protection of older people lies primarily in acclimatization and the appropriate use of air-conditioning or circulating or ventilating fans in the home, or in the living room or bedroom when needed. In general, older people prefer and thrive better in a climate which is warm all the year around, provided they are equipped to handle occasional extremes of temperature and humidity which might subject them to unacceptable levels of environmental stress, rather than a climate which includes extremes of cold in wintertime.

The available evidence suggests that healthy older persons, that is to say, persons who have survived long enough to become old, a selected group, are capable of developing heat acclimatization and physical conditioning when exposed to warmer conditions and more strenuous activities than those to which they are normally accustomed in much the same way as younger persons (Cole and Lyczkowskj, 1967; Henschel, Cole, and Lyczkowskj, 1968). Moderate levels of physical and environmental stress do not appear to restrict adaptive capacity severely in the middle aged provided they are in good heath (Dill and

Consolazio, 1962; Robinson, Belding, Consolazio, Horvath, and Turrell, 1965) although older men and women are not so tolerant of work-climate combinations verging on the upper limits of human tolerance (Lofstedt, 1966).

The sick do not fare so well. Macpherson, Ofner and Welch (1967) related the numbers of daily deaths at an institute for aged and invalid people in the suburbs of Sydney, Australia, to the daily air temperature recorded at 3 PM in the shade between 1 October 1962 and 31 December 1963. The effect varied with age and in the 80–89-year age group the comparatively warm temperature range 70–79°F (21.1–26.1°) was associated with a marked reduction in daily mortality and was clearly the most favorable temperature condition. They concluded that from the age of 70 onward there was a progressive decrease in the ability of this institutionalized community to adjust to changes in environmental temperature. It is thus probable that the high mortality rate from heat illness in the older age groups cannot be ascribed primarily to lack of acclimatization. The most likely explanation lies in the excessive demands made on the aging cardiovascular and cerebrovascular systems.

Diabetes

It was surprising that the death rate for diabetics should go up during the summer months. The first explanation which came to mind was that the association of arteriosclerosis with diabetes accounted for the deaths in much the same way as for excess deaths from arteriosclerosis of the heart and brain. However, Green's (1967) observation at St. Louis in 1966 that abnormally high blood sugars were not uncommon in nondiabetic heat-stroke cases raises the possibility that there may be some other factor, possibly a direct thermal stress-endocrine relationship which has not been recognized hitherto and which might call for additional supervision and therapeutic cover during heat waves or unusually warm weather falling short of a heat wave. One clue to the underlying pathology may lie in the observations of Bleisch (1967) who autopsied 14 heat-stroke cases and reported subtle changes in the liver including depletion of glycogen, and changes in mitochondria which he considered indicative of a deficit in oxidative phosphorylation. On the evidence available, further observation of diabetics during hot weather might prove enlightening.

Diagnostic Criteria

The grouping together of all causes of death from heat and insolation under rubric E931 in the General Mortality Tables conveniently avoids the need to consider the diagnostic criteria for heat stroke and heat exhaustion which have recently been questioned by Shibolet and his colleagues (1967). They reject cessation of sweating and body temperatures on admission to hospital in excess of 106°F (40°) as diagnostic yardsticks for heat stroke and the assumption that heat stroke only occurs in hot climates. On the other hand, when the appropriate laboratory facilities are available and the measurements can be made shortly after the onset of illness, they found that elevated levels of some or all serum enzymes invariably occur in cases of heat stroke, the diagnosis being seriously in doubt in patients showing normal values. They considered profound disorders

of clotting the most sinister clinical and pathological aspect and presumed it to be the cause of death in all fatal cases. The application of more elastic yet more precise, criteria than some authorities have recommended in the past should clarify this diagnostic enigma.

Air-Conditioning

Air-conditioning provides the first line of defense against excessive warmth, provided installations are designed to cope with the most severe conditions which are likely to occur, provided they are operated and maintained efficiently and that the available power supplies are adequate to ensure that they will continue to function to maximum capacity during severe heat waves when there is an optimum strain on the machinery as well as on the people who are exposed to thermal stress. Those who lead an air-conditioned life are, however, less likely to become acclimatized to summer heat than those who do not and they will be more prone to suffer adverse effects if artificial means for controlling heat and humidity should be withheld.

TABLE XIV

Heat-Stressful Environments in the United States (by States)[a]

State	Mean Maximum Seasonal Temperatures, °F			No. of Cities Represented
	T_{db}[c]	T_{wb}[c]	T_{eff}[b]	
Alabama	97	80	86	9
Alaska	71	61	68	6
Arizona	101	71	83	9
Arkansas	99	80	86	7
California	94	75	83	61
Colorado	92	64	78	13
Connecticut	90	77	82	8
Delaware	93	79	84	2
District of Columbia	94	78	84	2
Florida	93	80	85	23
Georgia	97	79	85	19
Hawaii	86	74	80	4
Idaho	95	66	79	9
Illinois	95	78	84	27
Indiana	94	78	84	24
Iowa	94	78	84	16
Kansas	100	76	85	16
Kentucky	95	79	85	10
Louisiana	96	81	86	11
Maine	87	74	80	7
Maryland	94	78	84	6
Michigan	89	75	81	21
Massachusetts	89	75	81	13
Mississippi	97	80	86	18
Missouri	97	79	85	14
Montana	91	66	78	14
Nebraska	96	75	83	14
Nevada	96	64	79	9

TABLE XIV (*Continued*)

State	Mean Maximum Seasonal Temperatures, °F			No. of Cities Represented
	T_{db}[c]	T_{wb}[c]	T_{eff}[b]	
New Hampshire	89	75	81	7
New Jersey	93	77	83	8
New Mexico	96	68	80	17
New York	89	75	81	35
North Carolina	94	79	85	17
North Dakota	93	73	82	8
Ohio	92	77	83	30
Oklahoma	102	78	86	16
Oregon	91	67	79	15
Pennsylvania	91	76	82	22
Rhode Island	87	75	80	2
South Dakota	95	76	84	9
South Carolina	96	79	85	12
Tennessee	96	78	85	13
Texas	99	78	86	49
Utah	96	66	80	10
Vermont	87	74	80	3
Virginia	94	79	85	11
Washington	79	67	74	18
West Virginia	90	76	82	10
Wisconsin	89	76	82	16
Wyoming	89	63	77	11

[a] Figures are near-peak values exceeded only 1% of the summer months (June–September) as taken from long time records of the United States Weather Bureau.

[b] For sedentary, lightly clothed persons in the United States; air movement 20 ft/min (from ASHRAE Handbook of Fundamentals, 1967).

[c] Mean simultaneous Design Temperatures for summer coding of indoor air (i.e., air conditioning) in all major cities of each state.

Notes

a. Acclimatized healthy men wearing warm-weather clothing engaged in daily *sedentary activities* can tolerate an Effective Temperature (T_{eff}) of 85°.

b. Effective temperatures of 66–75° are in the Comfort Zone

c. Number of states having $T_{eff} \geq 86°$ = 6 (12%)
Number of states having $T_{eff} \geq 85°$ = 15 (30%)
Number of states having $T_{eff} \geq 84°$ = 22 (44%)
Number of states having $T_{eff} \geq 83°$ = 27 (54%)
Number of states having $T_{eff} \geq 82°$ = 32 (64%)
Number of states having $T_{eff} \geq 81°$ = 36 (72%)
Number of states having $T_{eff} \geq 80°$ = 42 (84%)
Number of states having $T_{eff} \geq 79°$ = 45 (90%)
Number of states having $T_{eff} \geq 68°$ = 50 (100%)

d. Number of states having mean summer-season Effective Temperature in the Comfort Zone, i.e., T_{eff} = 66–75°: 2 (Alaska and Washington).

e. States having highest mean summer-season, T_{eff} = 86°: 6 (*viz.*, Alabama, Arkansas, Louisana, Mississippi, Oklahoma and Texas).

f. States having second highest mean summer-season, T_{eff} = 85°: 9 (*viz.*, Florida, Georgia, Kansas, Kentucky, Missouri, North Carolina, South Carolina, Tennessee, and Virginia).

g. States having lowest mean summer-season T_{eff} (<80°): 8 (*viz.*, Alaska, Colorado, Idaho, Montana, Nevada, Oregon, Washington, and Wyoming).

The American Society of Heating, Refrigerating and Air-Conditioning Engineers (1967) recommends for design purposes for each state simultaneously occurring heat-stressful dry- and wet-bulb temperatures out of doors which, according to the long-term records of the United States Weather Bureau, are likely to be exceeded on the average for only 1% of the summer months, June–September. These temperatures are listed in Table XIV with effective temperatures computed from the Normal Effective Temperature Chart (Houghten and Yaglou, 1924) by Rapp (1971) for "still-air" conditions, the conditions recommended by the Society as the basis for the design of air-conditioning units and installations for sedentary and lightly clothed persons.

The mean maximal, seasonal effective temperatures in this table equal or exceed the optimum of 83°F for comfort recommended for the southern United States by this Society (1942) many years ago as the upper level to allow for in the design of climate-control equipment for homes and offices in 27 states. If more strenuous work is to be performed for more than a short period, or more clothing than usual is to be worn, the indoor design temperature will be lowered by a margin corresponding to the amount of clothing and the average energy consumption entailed by the activity.

The Handbook of Fundamentals (1967), from which these temperatures were abstracted, recommends that manufacturers who wish to meet more stringent requirements for the "one hottest season in fifty" (years) at any design level should add the difference between the average 5% level temperature and the average 1% level, both of which are given in the Handbook, though not in this table. This would give an upper design outdoor dry-bulb temperature, for example, of 104°F (40°) for St. Louis Airport, Missouri, a level which was exceeded by an appreciable margin, not infrequently, during the past 2 decades.

The requirements for those who live today in air-conditioned homes, work in air-conditioned offices or other public buildings and travel to and fro in air-conditioned private or public transport must allow for the fact that these people are likely to be less acclimatized than the populations on whom the classical studies to determine the thermal comfort requirements of United States citizens in their homes or offices were carried out 30–50 years ago. An analogous situation exists in warships today in which the very great majority of living and working spaces between decks are air-conditioned, whereas they were not in the days when the upper desirable effective temperatures to be allowed for in ship design to cover operations in warm climates were last determined, slightly less than 30 years ago. It has now been recommended that the maximum upper effective temperature in air-conditioned living, messing, hospital, office and control spaces for design purposes should be reduced from the former design level of 78°F (25.6°) effective temperature to 74°F (23.3°) (United States Navy Department, 1965).

The extent to which living an air-conditioned existence detracts from natural acclimatization to living and working at high temperatures and modifies the optimum levels of warmth for those who lead an air-conditioned life in the summer months and the upper levels of warmth which they can be expected to tolerate in emergency without sustaining ill effects have still to be determined.

Air Movement

Prior to the nationwide use of air-conditioning the first line of defense against summer heat was to take full advantage of natural and artificial cooling breezes by the sound location and construction of dwellings and work places and by the generous use of a variety of fans for ensuring a good circulation of turbulent air. The air-conditioning engineers, however, have a stated design requirement that air movement in air-conditioned apartments and other buildings should only be of the order of 20–40 feet per minute—virtually a "still air" condition which becomes intolerable if the air-conditioning fails for any reason, for example, an unavoidable enforced power cut or a strike of workers in the power stations and associated services during even moderately warm weather, let alone the very severe heat-wave conditions which have occurred in various parts of the United States during the present century.

An acquaintance who lived in Kansas City during the 1934 and 1936 heat waves in an old fashioned, non-air-conditioned apartment which was, however, built to take full advantage of natural cross ventilation with large, well-positioned windows, remarked that it was always possible to come to terms with temperatures exceeding 100°F (37.8°) for much of the summer making full use of natural ventilation and the air circulation which could be provided by fans. Whereas, during the "brown-out" and the mild heat wave in Washington, D. C. in September 1970, when the temperatures were almost identical with those which occurred in New York City, conditions in a modern air-conditioned apartment when the air-conditioning failed were quite intolerably warm because of the complete lack of air movement and one could not wait to get dressed and get out in the streets to obtain relief. People living and working in the more robustly constructed old fashioned apartments and other buildings which were not air-conditioned, but which were built and equipped to take advantage of natural and artificial air movement, were more comfortable and able to cope and they were probably better acclimatized to the warmth of the Washington summer than the air-conditioned populace. This recollection raises two questions. First, is the air-conditioned population today less well acclimatized in summer than the very largely non-air-conditioned population of the mid-thirties? Second, is the importance of ensuring adequate air movement in the absence of effective air cooling and dehumidification generally recognized and taken into consideration by those responsible for climate control?

The remarkably adverse effects of "still air" (20–30 ft/min, 0.1–0.15 m/s) on ability to do physical work and the contrasting beneficial effects of even barely perceptible air movement (200 ft/min, 1.0 m/s) under hot and humid conditions have been established experimentally (Dunham *et al.*, 1946; Ellis *et al.*, 1953) and so have the adverse effects on comfort which are greatly alleviated by increasing air movement even to just perceptible levels (Ellis, 1952) but the practical applications of this research have attracted little attention. Some compromise would seem to be necessary to ensure that when air-conditioning systems fail, either because of inefficient design, operation or maintenance, or because of unusually severe seasonal warmth occurring at a time when the power supplies

have been reduced, the adverse effects can be ameliorated by the optimum use of natural and artificial air movement.

Need for an Unbiased Reevaluation

There is a pressing need for an unbiased evaluation of the situation in the light of the changes of the past 30 years and the resources available today, to consider man's fundamental requirements for both natural and artificial climate control in the modern context with full regard to geographical considerations, the economy of the individual and the community at large, available power supplies and a world which has warmed up during the present century and which, according to the latest consensus of informed opinion (SCEP, Massachusetts Institute of Technology, 1970), may be expected to warm up even more during the next 30 years, because of such factors as vast increases of heat generated on the earth's surface, increasing concentrations of carbon dioxide in the atmosphere and possibly the pollution of the stratosphere by increasing numbers of supersonic aircraft.

As cities get larger they warm up and the general tendency is for cities to grow and probably, in the future, to coalesce. Architects are now advising the construction of fully-air-conditioned homes with windows which cannot be opened, and this is already the practice in the construction of many large stores and public buildings, all of which are at the mercy of the power supplies and could become death traps for some if there were power cuts during a severe heat wave, or if air-conditioning policy is determined by the calendar not by the ambient temperature and humidity.

Morbidity

When there is an abnormally high incidence of heat deaths in a community the morbidity due to heat and the adverse effects on efficiency, comfort and well-being are considerable at all ages. In 1944 and 1945 in the excessively hot, non-air-conditioned living and working spaces of the ships of the British Eastern and Pacific Fleets there were practically no deaths due to heat but prolonged exposure to the most severe and unremitting warmth ever recorded for such a large community doubled the attendances at the sick bay and the effects on efficiency and on comfort were profound (Critchley, 1945, 1947; Ellis, 1945, 1947, 1948, 1953). Weekly sickness returns from all ships carrying a medical officer after the War were analyzed to show that minor sickness was 3–4 times greater in tropical than in northern temperate waters (Roberts, 1948) and the percentage of ships' companies attending for treatment increased as the weather became warmer, particularly when the average air temperature recorded on the upper deck at noon exceeded 80°F (26.7°) which corresponded approximately to an average effective temperature in the living spaces of about 80°F (Ellis, Smith and Underwood, 1953; Smith, 1958).

Many cases of acute heat illness are transient and are never seen by a doctor. Others have recovered by the time they are seen and no record is kept but at the time a person may be completely incapacitated, unconscious or completely incompetent, possibly a danger to others and certainly unable to carry on with his or her work.

Some idea of the true incidence of recognizable heat illness in the lay community in an area where heat illness is endemic has been provided by Schuman (1962) who reported that 18 of 192 persons (9%), aged 3–90, in the Tecumseh Community Health Study replied "yes" to the question "Have you ever had a sunstroke or a heatstroke?" When Austin and Berry selected 100 heat-stroke cases out of 1,000 cases of heat illness for review they did not give the death rate among the group as a whole but they did comment that there were only 12 deaths among 53 patients who were comatose when admitted. A person who is comatose from heat may well sustain temporary or permanent neurological deficit or other organic damage and be more prone to suffer adversely from exposure to excessive warmth on future occasions. Cook (1955) reported 2,001 heat illness cases in 6 United States Army posts in 1954. There were only 20 cases of heat stroke and only one man died, although one other man developed severe neurological changes which necessitated his discharge from the Army. For the moment, all that can be said of morbidity in the civil population during heat waves is that it must be very considerable. It is an unknown quantity and is likely to be more severe and more diffuse in an aging population, among sick people and infants and others who cannot look after themselves.

CONCLUSIONS

A. Examination of the Vital Statistics Reports of the United States Public Health Service for the years 1952–1967 permits the following conclusions to be drawn.

1. Heat waves causing an appreciable number of deaths which were tabulated as due to the effects of excessive heat and insolation occurred sporadically in about half the states in one year or another.

2. More than 500 deaths per annum were tabulated as due to excessive heat and insolation in 1952, 1953, 1954, 1955 and 1966.

3. The majority of heat deaths were reported in July in 1954, 1955 and 1966, and in June in 1952. In 1953 the deaths were spread over a 5-month period—more than 100 deaths in June, July and September and 79 in August.

4. Since 1949 it has been the practice to code excessive heat and insolation as a cause of death only if there were no other coexistent pathological condition such as heart disease; and, except in the relatively uncommon clear-cut deaths from heat stroke or heat exhaustion, certifying medical officers tend to avoid death due to excessive heat as a primary, or even as a secondary, diagnosis. Thus, many deaths which are primarily due to heat are not certified as such and of those which are certified many are coded under other rubrics than excessive heat and insolation (E931) and go to swell the numbers of deaths from all causes. The latter provide a more accurate measure of the effect of a heat wave on mortality in any single month than the numbers of heat deaths alone.

5. During the 5 heat-wave years 1952–1955 and 1966 excess deaths due to heat-aggravated or heat-precipitated illness during the heat wave were at a conservative estimate at least 10 times as numerous as those which were tabulated as due to excessive heat in the General Mortality Tables.

6. In either June or July there were excess numbers of deaths due to vascular accidents of the central nervous system in 1952–1955 and 1966 and similar but smaller excess numbers of diabetic deaths in 1952, 1954, 1955 and 1966, while over the entire period there was on average a July increase in the number of deaths due to "certain diseases peculiar to infancy" and "senility without mention of psychosis."

7. Excess deaths from arteriosclerotic and degenerative heart disease, including coronary disease, were observed in 1955 and 1966 and there was an excess of deaths from hypertensive heart disease in May, June or July in each of the heat-wave years but not in 10 of the other 11 years.

8. The distribution of deaths due to excessive heat and insolation by age reveals that more deaths of infants under 1 year of age were tabulated than for any other 1-year age group, in all probability, although the figures for a single year (as opposed to 5 or 15 years) are only available for infants. However, calculation of the death rates revealed that, whereas below 50 years of age the heat-death rate was higher in infants than any other age group, above 50 years of age the rate becomes higher in adults and progressively so with advancing years.

9. Deaths of males were more numerous than deaths of females in both the white and the nonwhite population. The proportions of nonwhite persons who were tabulated as having died from excessive heat and insolation were rather more than twice as great as the proportions of white persons for both sexes.

10. The heat wave in 1952 was the most extensive and severe in recent years and the numbers of deaths from excessive heat reached proportions which exceeded by a large margin the death toll in any nonclimatic peacetime disaster in this country in modern times. The largest number of excess deaths from all causes during the past 20 years occurred, however, during the less severe heat wave in July 1966 which was more localized.

11. Between 1952 and 1967 the largest number of heat deaths were tabulated for Missouri, Texas, California and Illinois but for the 4-heat-wave years, 1952–1955, the heat-death rate was more than 4/100,000 in Missouri, whereas, it was less than 1/100,000 in California and Texas, 11 other states having higher rates than Texas as well as Missouri and 23 other states having higher rates than California.

B. Scrutiny of the New York City Health Department's daily records of deaths by day of occurrence and the Environmental Data Service's daily Climatological Data Summaries reveals that during a minor heat wave toward the end of September 1970, when there were electrical power cuts on the East Coast, there were significantly more deaths in New York City than on any other day in this month or on any day except for 2 during the next 4 months. The implications are discussed.

C. The increasing installation of air-conditioning in old and new construction of all types, and particularly in the "heat-wave states," provide the first line of defense during heat waves against heat stroke, heat exhaustion, heat-aggravation of known diseases or sudden precipitation of heat deaths in persons with latent disease. It is of primary importance that across the country, and particularly

in those areas where heat waves are likely to occur, the location and capacity of generating stations should be planned to ensure that cooling and dehumidifying installations can operate efficiently under the hottest and most humid ambient conditions which past experience shows are likely to be encountered in the future and that policies are framed to ensure that adequate power supplies will be available to ensure their efficient operation. If power supplies fail, occupants of air-conditioned homes, workplaces and other public buildings will be much more vulnerable to heat injury than before the days of air-conditioning and disaster situations with a high excess mortality will result.

ADDENDUM

The number of certified deaths from excessive heat and insolation in Table X, while they show the actual death toll among infants and the aged in relation to other age groups, are uncorrected to allow for the numbers at risk in the different groups. Rates per 100,000 were calculated using the Population Estimates for the different age groups given in Vital Statistics Volume I for the years 1952–1955 and in the Bureau of the Census Statistical Abstract for 1966 and are shown in Table XV for 5 years when there were more than 300 heat-certified deaths.

These rates show that, according to heat-death certifications, infants below 1 year of age are the most heat illness-prone age group below 50-years of age but above 50-years of age adults are more heat illness-prone than infants and become progressively so with advancing age. With the exception of the 5–19-age group in 1955, the death rate was greater for all age groups from 1952–1955 than in 1966.

ACKNOWLEDGMENTS

I am deeply indebted to Professor James D. Hardy who suggested this study and provided me with the opportunity to carry it out; to Professor Colin White, Dr. Robert J. Hardy and Dr. Steven P. Bayard of the Department of Biometry, Yale School of Medicine and Dr. I. M. Moriyama of the National Statistical Office for statistical advice and assistance; and for most generous assistance, advice and criticism to Brigadier B. G. Holzman, Mr. H. C. S. Thom and Mr. W. H. Haggard of the National Oceanic and Atmospheric Administration Environmental Data Service; Dr. E. Ferrand of the New York City Department of Air Resources; Mr. C. Couchman of the Division of Air Pollution Control, Washington, D. C.; Mr. Louis Pincus and Miss Frieda Nelson of the City of New York Department of Health's Statistical Service and Mr. Roberto Fuentes, Chief, Department of Biostatistics, Washington, D. C.; my colleague Mr. G. M. Rapp; Dr. D. H. K. Lee and the following participants in

TABLE XV

DEATHS FROM "EXCESSIVE HEAT AND INSOLATION"—BY AGE—UNITED STATES 1952–1955, 1966. RATES PER 100,000

Age and Year	Total	Under 1 year	Under 5 years	5–19 years	20–34 years	35–49 years	50–64 years	65–79 years	Over 80 years	Not stated
1952	0.90	2.12	0.56	0.06	0.27	0.76	1.57	3.42	11.5	(3)
1953	0.36	0.64	0.18	0.05	0.14	0.30	0.75	1.15	3.88	(5)
1954	0.61	1.61	0.39	0.02	0.14	0.39	0.85	2.46	11.78	(3)
1955	0.37	0.58	0.15	0.01	0.07	0.36	0.74	1.45	4.27	(3)
1966	0.27	—	0.09	0.02	0.06	0.21	0.47	1.51		—
Total	0.49	1.23	0.27	0.03	0.14	0.40	0.85	2.11(4)	7.8(4)	(14)

the National Institute of Environmental Health Sciences' Workshop on Mortality from Heat Illness: Mr. C. A. Bridger, Dr. T. D. Downs, Mr. J. F. Clarke, Dr. Austin Henschel, Dr. S. H. Schuman and Dr. R. W. Buechley. Lastly, I am most deeply indebted to my secretary, Mrs. Nathan Frank, for her infinite patience and expert typing of numerous drafts and most loyal assistance at every stage of this investigation.

REFERENCES

American Society of Heating and Ventilating Engineers Research Technical Advisory Committee (1942). Sensations of Comfort. 48th Annual Meeting, Paper 1196.

American Society of Heating, Refrigerating, Ventilating and Air-conditioning Engineers (1967). Handbook of Fundamentals.

Austin, M. G. and Berry, J. W. (1956). Observations on 100 cases of heat stroke. *J. Amer. Med. Assoc.* **161**, 1525–1529.

Barry, M. E. and King, B. A. (1962). Heatstroke. *S. Afr. Med. J.* **36**, 455.

Bleisch, V. R. (1967). Heatstroke; Pathogenesis of acute phase and complications of chronic phase. *Proc. Joint Annl. Meet. Amer. Soc. Clin. Pathol. Coll. Amer. Pathol.*

Boyd, J. T. (1960). Climate, air pollution and mortality. *Brit. J. Prev. Soc. Med.* **14**, 123.

Bridger, C. A. and Helfand, L. A. (1968). Mortality from heat during July, 1966, in Illinois. *Int. J. Biometeorol.* **12**, 41–70.

Brown, E. G. (1935). Deaths from excessive heat in Kansas, 1934. *Pub. Health. Rep. (U. S.)* **50**, 546.

Buechley, R. W. (1971A). Heat island equals death island? Report from the Epidemiological section, Ecological Research Branch, Division of Health Effects Research, Air Pollution Control Office, North Carolina.

Buechley, R. W. (1971B). Unpublished presentation to National Institutes of Health Workshop on Heat and Mortality, National Institute of Environmental Health Sciences, North Carolina, 28–29 April 1971.

Burch, G. E., and DePasquale, N. P. (1962). Hot climates; man and his heart. Thomas, Springfield, Illinois.

Burch, G. E. and Ansari, A. (1968). Artificial acclimatization to heat in control subjects and patients with chronic congestive heart failure at bed rest. *Amer. J. Med. Sci.* **256**, 180.

Burch, G. E. and Miller, G. C. (1969). Effects of warm, humid environment on patient with congestive heart failure. *Southern Med. J.* **62**, 816.

Burch, G. E. and Giles, T. D. (1970). The burden of a hot and humid environment on the heart. Modern Concepts Cardiovascular Disease **8**, 115.

Bureau of the Census, U. S. Dept. of Commerce (1906). Special Report: Mortality, 1900–1904.

Bureau of the Census, U. S. Dept. of Commerce (1934). Vital Statistics: Special Report.

Bureau of the Census, U. S. Dept. of Commerce (1966). Population Estimates: Series P25, 304, 354, 373.

Cardullo, H. M. (1949). Sustained summer heat and fever in infants. *J. Pediat.* **35**, 24.

Cole, M. B. and Lyczkowskyj, O. (1967). An experimental group of senior citizen volunteers. *J. Amer. Geriat. Soc.* **15**, 82–86.

Cook, E. L. (1955). Epidemiological approach to heat trauma. *Mil. Med.* **116**, 5, 317–322.

Council on Environmental Quality (1970). First Annual Report of the Council on Environmental Quality. U. S. Printing Office Washington, D. C.

Critchley, M. (1945). Problems of naval warfare under climatic extremes. *Brit. Med. J.* **145**, 173.

Critchley, M. (1947). Effects of climatic extremes. *Brit. J. Ind. Med.* **4**, 164.

Danks, D. M., Webb, D. W. and Allen, J. (1962). Heat illness in infants and young children; a study of 47 cases. *Brit. Med. J.* **5300**, 287.

Department of Defense (1969). The etiology, prevention, diagnosis and treatment of the adverse effects of heat. Departments of the Army, Navy and Air Force. T B Med **175**, NAVMED D-5052–5, AFP, 160–1.

Department of Public Health: State of California (1956). Second report of the State of California on the air pollution study project: Clean air for California, March 1955.

DEPASQUALE, N. P. AND BURCH, G. E. (1961). The seasonal incidence of myocardial infarction in New Orleans. *Amer. J. Med. Sci.* **240**, 4, 124.

DILL, D. B. AND CONSOLAZIO, C. F. (1962). Responses to exercise as related to age and environmental temperature. *J. Appl. Physiol.* **17**, 645.

DUNHAM, W., HOLLING, H. E., LADELL, W. S. S., MCARDLE, B., SCOTT, J. W., THOMSON, M. L. AND WEINER, J. S. (1946). The effects of air movement in severe heat. *Med. Res. Counc. London*, Rep. RNP **46**, 316.

ELLIS, F. P. (1945). First report of the habitability mission to the Eastern Fleet:1944. *Med. Res. Counc. London*, Rep. RNP **45**, 202.

ELLIS, F. P. (1947). The effect of environment on the health and efficiency of men in warships. M.D. Thesis. Library of Medical School, University of Manchester.

ELLIS, F. P. (1948). Environmental factors influencing health and efficiency in warships. *Brit. Med. J.* **1**, 587.

ELLIS, F. P. (1952). Thermal comfort in warm and humid atmospheres. Observations in a warship in the tropics. *J. Hyg. Cambridge* **50**, 415.

ELLIS, F. P., SMITH, F. E. AND UNDERWOOD, C. R. (1953). The effects of upper deck temperature on the health of men in ships of the Royal Navy. *Brit. J. Prev. Soc. Med.* **7**, 69.

ELLIS, F. P., FERRES, H. M., LIND, A. R. AND NEWLING, P. B. (1953). The upper tolerable levels of warmth for acclimatized men working in the tropics. *Med. Res. Counc., London* Rep. RNP **53**, 759.

ELLIS, F. P. (1953). Tolerable and desirable levels of warmth in warm climates with special reference to the requirements of men in the Royal Navy. Hunterian Lecture. *Ann. Roy. Coll. Surg. Engl.* **13**, 369.

ELLIS, F. P. (1955). Prevention of heat incapacitation in the Armed Forces. *Mil. Med.* **116**, 5, 323.

FERGUSON, M. AND O'BRIEN, M. M. (1960). Heat stroke in New York City; experience with 25 cases. *N. Y. State J. Med.* **2531–2538.**

FERRIS, E. B., BLANKENHORN, M. A., ROBINSON, H. W. AND CULLEN, G. E. (1938). Heat stroke; clinical and chemical observations on 44 cases. *J. Clin. Invest.* **17**, 249.

FLOREY, C.DUV., SENTER, M. AND ACHESON, R. (1967). A study of the validity of the diagnosis of stroke in mortality data. *Yale J. Biol. Med.* **40**, 2, 148.

FRIEDFELD, L. (1949A). Prophylaxis and treatment of heat-reaction states. *N. Engl. J. Med.* **240**, 26, 1043.

FRIEDFELD, L. (1949B). Heat reaction states in the aged. *Geriatrics* **4**, 211.

FUENTES, R. (1971). Department of Health (Biostatistics), Washington, D. C. Personal communication.

GAUSS, H. AND MEYER, K. A. (1917). Heat stroke: report of 158 cases from Cook County Hospital, Chicago, Illinois. *Amer. J. Med. Sci.* **154**, 554.

GOVER, M. (1938). Mortality during periods of excessive temperature *Pub. Health. Rep. (U. S.)* **53**, 1122.

GREEN, W. L. (1967). In discussion of "A 65 year old woman with heatstroke", by Aach, B. and Kissane, J. *Amer. J. Med.* **43**, 117.

HAGGARD, W. H. (1971). Personal communication.

HALDEN, E. R., JONES, F., SUTHERLAND, D. A. AND MUIRHEAD, E. E. (1955). Hematologic studies in heat stroke: the anemia of heat stroke with emphasis on a hemolytic component. *Southern Soc. Clin. Res.* **141.**

HARDIN, G. (1971). Nobody ever dies of over-population. *Science* **171**, 527.

HARDY, J. D. (1971). Thermal comfort and health. *Amer. Soc. Heat. Refrig. Air-Cond. Eng. J.* **43**, 51.

HELFAND, L. A. AND BRIDGER, C. A. (1971). Hippocrates, thermal stress and stroke mortality. Weatherwise (in press).

HENSCHEL, A., COLE, M. B. AND LYCZAOWSKYJ, O. (1968). Heat tolerance of elderly persons living in a subtropical climate. *J. Gerontol.* **23**, 1, 17.

HENSCHEL, A., BURTON, L., MARGOLIES, L. AND SMITH, J. E. (1969). An analysis of the heat deaths in St. Louis during July 1966. *Amer. J. Pub. Health* **59**, 12, 2232.

HEXTER, A. C. AND GOLDSMITH, J. R. (1971). Carbon monoxide: association of community air pollution with mortality. *Science.* **172**, 265.

HEYER, H. E., TENG, H. C. AND BARRIS, W. (1953). The increased frequency of acute myocardial infarction during summer months in a warm climate. *Amer. Heart J.* **45**, 741.

HOUGHTEN, F. C. AND YAGLOU, C. P. (1942). Cooling effect on human beings produced by various air velocities. *Amer. Soc. Heat. Vent. Eng. Trans.* **29**, 163.

Illinois Dept. of Health (1968). Vital Statistics, Illinois, 1966.

KESSLER, W. R. AND ANDERSEN, D. H. (1951). Heat prostration in fibrocystic disease of the pancreas and other conditions. *Pediatrics* **8**, 648.

KUTSCHENREUTER, P. H. (1959). A study of the effect of weather on mortality. *Trans. N. Y. Acad. Sci.* **22**, 126–138.

LAVE, L. B. AND SESKIN, E. P. (1970). Air pollution and human health. *Science* **169**, 3947, 723.

LEE, D. H. K. (1971). Personal communication.

LEVINE, J. A. (1969). Heat stroke in the aged. *Amer. J. Med.* **47**, 251–256.

LOFSTEDT, B. (1966). Human heat tolerance. Dept. Hyg. Univ. Lund, Lund, Sweden 70. Library of Congress.

LOGAN, W. P. D. (1953). Mortality in the London fog incident. *Lancet* **1**, 336.

MALAMUD, N., HAYMAKER, W. AND CUSTER, R. P. (1946). Heat stroke: a clinico-pathological study of 125 fatal cases. *Mil. Med.* **99**, 397.

MACPHERSON, R. K., OFNER, F. AND WELCH, J. A. (1967). Effect of prevailing air temperature on mortality. *Brit. J. Prev. Soc. Med.* **21**, 1, 17.

MINARD, D. (1961). Prevention of heat casualties in Marine Corps Recruits. *Mil. Med.* **126**, 4, 261.

MINARD, D., BELDING, H. S. AND KINGSTON, J. R. (1957). Prevention of heat casualties. *J. Amer. Med. Ass.* **165**, 1813.

National Center for Health Statistics, U. S. Dept. of Health Education Welfare (1949). Vital Statistics.

National Center for Health Statistics, U. S. Dept. of Health Education Welfare (1952–1967). Vital Statistics of the United States, Vol. II.

NELSON, F. (1970). New York City Dept. of Health. Personal communication.

NELSON, F. (1971). New York City Dept. of Health. Personal communication.

National Oceanic and Atmospheric Administration Environmental Data Service (NOAA) (1970A). Local Climatological Data; Central Park, New York City, September.

National Oceanic and Atmospheric Administration Environmental Data Service (NOAA) (1970B). National Airport, Washington, D. C. September.

National Oceanic and Atmospheric Administration Environmental Data Service (NOAA) (1971). National Capital Area. Climatic Summary. September.

OECHSLI, F. W., AND BUECHLEY, W. B. (1970). Excess mortality associated with three Los Angeles September hot spells. *Environ. Res.* **3**, 277.

RAPP, G. M. (1971). Personal communication.

REYBURN, T. L. (1855). Diseases of Missouri and Iowa. *Trans. Amer. Med. Ass.* **8**, 223–320.

ROBERTS, J. A. F. (1948). Returns of sickness from ships of the Royal Navy 1945–1946; a contribution to medical climatology. *Brit. J. Prev. Soc. Med.* **2**, 55.

ROBINSON, S., BELDING, H. S., CONSOLAZIO, C. F., HORVATH, S. M. AND TURRELL, E. S. (1965). Acclimatization of older men to work in heat. *J. Appl. Physiol.* **20**, 563.

ROGOT, E. AND BLACKWELDER, W. C. (1970). Associations of cardiovascular mortality in Memphis, Tennessee with weather. *Pub. Health* **85**, 25.

ROOT, C. J. (1937). Deaths during the heat wave of July 1936 at Detroit. *Bull. Amer. Meteorol. Soc.* **18**, 232–236.

ROSE, G. (1966). Cold weather and ischaemic heart disease. *Brit. J. Prev. Soc. Med.* **20**, 97.

ROSENWAIKE, I. (1966). Seasonal variation of deaths in the United States, 1951–1960. *Amer. Statist.* **61**, 315, 706–719.

"SCEP"-Massachusetts Institute of Technology (1970). Man's impact on the global environment; report of the study of critical environmental problems. M.I.T. Press, Cambridge, Massachusetts.

SCHICKELE, E. (1947). Environment in fatal heatstroke; an analysis of 147 cases occurring in the Armed Forces in the United States during World War II. *Mil. Surg.* **98**, 43.

SCHRIER, R. W., HENDERSON, H. S., TISHER, C. C., AND TANNEN, R. L. (1967). Nephropathy associated with heat stress and exercise. *Ann Int. Med.* **67**, 356.

SCHUMAN, S. H. (1962). Population studies of human sweat and the evaluation of a proposed screening test for cystic fibrosis of the pancreas. Dr. P. H. Thesis, Library Univ. Mich. Sch. Pub. Health., Dept. Epid.

SCHUMAN, S. H. (1962). Host factors and environment in studies of human sweat. *Ind. Med. Surg.* **31**, 10, 443–449.

SCHUMAN, S. H. (1967). Effects of heat waves on mortality in St. Louis, New York and the Midwest in 1966. Abstr. Joint Ann. Meet. Amer. Meteor. Soc. Amer. Geophys. Union. *Trans. Amer. Geophys. Union* **48**, 118.

SCHUMAN, S. H. (1971). Unpublished presentation to National Institutes of Health Workshop in Heat and Mortality, National Institute of Environmental Health Sciences, North Carolina 28–29 April, 1971.

SCHUMAN, S. H. (1971). Diabetes incidence during a heat wave in New York, 1966. Personal communication.

SCHUMAN, S. H., ANDERSON, C. P. AND OLIVER, J. T. (1964). Epidemiology of successive heat waves in Michigan in 1962 and 1963. J. Amer. Med. Ass. 733–738.

SCOTT, J. A. (1953). Fog and deaths in London, December 1952. *Pub. Health Rep. U. S.* **474**.

SHATTUCK, G. C. AND HILFERTY, M. M. (1932). Sunstroke and allied conditions in the United States. *Amer. J. Trop. Med.* **12**, 223.

SHATTUCK, G. C. AND HILFERTY, M. M. (1933). Causes of death from heat in Massachusetts. *N. Engl. J. Med.* **209**, 319.

SHATTUCK, G. C. AND HILFERTY, M. M. (1936). Distribution of acute heat effects in various parts of the world. *N. Engl. J. Med.* **24**, 458.

SHIBOLET, S., FISHER, S., GILAT, T., BANK, H. AND HELLER, H. (1962). Fibrinolysis and hemorrhages in fatal heat stroke. *N. Engl. J. Med.* **266**, 169.

SHIBOLET, S., COLL, R., GILAT, T. AND SOHAR, E. (1967). Heatstroke: Its clinical picture and mechanism in 36 cases. *Quart. J. Med.* **36**, 144, 525.

SMITH, F. E. (1958). Climate and health in the Royal Navy. *Brit. J. Ind. Med.* **15**, 17.

Task Force on Research Planning in Environmental Health Science, U. S. Dept. of Health Education Welfare. (1970). Man's health and the environment; some research needs. U. S. Govt. Printing Office.

THOM, H. C. S. (1957). A new concept for cooling degree days. Air Cond. Heat. Vent. **54**, 6, 73.

U. S. Dept. of the Navy. (1965). Environmental control standards. OPNAV Instruction 9335.5A OP–36, Sept. 649 P30, 30 August.

Weather Bureau, U. S. Dept. of Commerce. (1900–1967). Monthly weather reviews.

Weather Bureau, U. S. Dept. of Commerce. (1952–1955, 1966). Climatological data.

Weather Bureau, U. S. Dept. of Commerce. (1940–1949). Climatological data. May–August, September–December.

World Health Organization. (1949). International Classification of Diseases, Injuries and Causes of Death, 1949. Revision. World Health Organization, Geneva, Switzerland.

World Health Organization. (1957). International Classification of Diseases, Injuries and Causes of Death, 1957. Revision. World Health Organization, Geneva, Switzerland.

WRIGHT, D. O., REPPERT, L. B. AND CUTTINO, J. T. (1946). Purpuric manifestations of heat stroke. *Arch. of Intern. Med.* 77, 27.

YAGLOU, C. P. (1956). Habitability studies in climatic extremes. Commission on Environmental Hygiene, U. S. Armed Forces Epidemiological Board, Ann. Rep. No. 9.

YAGLOU, C. P. AND MINARD, D. (1957). Control of heat casualties at military training centers. *Amer. Med. Ass. Arch. Ind. Health* 16, 302.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF TEXAS
HOUSTON DIVISION

STEPHEN McCOLLUM, and SANDRA McCOLLUM, individually, and STEPHANIE KINGREY, individually and as independent administrator of the Estate of LARRY GENE McCOLLUM,	§	
PLAINTIFFS	§	
	§	
v.	§	CIVIL ACTION NO.
	§	4:14-cv-3253
BRAD LIVINGSTON, JEFF PRINGLE, RICHARD CLARK, KAREN TATE, SANDREA SANDERS, ROBERT EASON, the UNIVERSITY OF TEXAS MEDICAL BRANCH and the TEXAS DEPARTMENT OF CRIMINAL JUSTICE.	§	JURY DEMAND
DEFENDANTS	§	

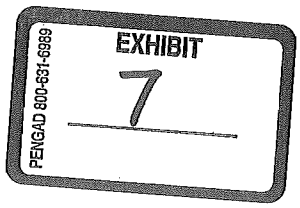
PLAINTIFFS' CONSOLIDATED RESPONSE TO DEFENDANTS' MOTIONS TO STRIKE SUMMARY JUDGMENT EVIDENCE

Exhibit F

HTN

Diabetes

Obesity



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Diagnosis of Diabetes

Silvio E. Inzucchi, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 42-year-old asymptomatic man with hypertension presents for his annual physical examination. His medications include atenolol combined with chlorthalidone (at doses of 50 mg and 25 mg, respectively, per day). Both parents had type 2 diabetes mellitus later in life. He does not smoke cigarettes. His body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) is 32.3, and his blood pressure is 130/80 mm Hg. Would you screen the patient for diabetes, and if so, how?

THE CLINICAL PROBLEM

From the Section of Endocrinology, Yale University School of Medicine, New Haven, CT. Address reprint requests to Dr. Inzucchi at the Section of Endocrinology, Yale University School of Medicine, 333 Cedar St., FMP-106, New Haven, CT 06520, or at silvio.inzucchi@yale.edu.

N Engl J Med 2012;367:542-50.
DOI: 10.1056/NEJMcp1103643

Type 2 diabetes is a complex disease that is typically diagnosed in midlife and is characterized by progressive defects in insulin secretion and action. In the context of increased caloric intake and decreased activity levels in Westernized societies, the prevalence of type 2 diabetes continues to climb. According to the Centers for Disease Control and Prevention, 25.8 million persons in the United States (or 8.3% of the population) have the disease, which is diagnosed in approximately 2 million persons each year.[1] Diabetes is usually silent in its initial stages, and irreversible complications may develop before treatment is begun.[2] Data from randomized trials indicate that early and aggressive antihyperglycemic therapy significantly reduces the risk of long-term microvascular complications.[2,3] Although the effects of tight glucose control on macrovascular disease are less clear,[4] the diagnosis of diabetes in a patient provides the opportunity to apply evidence-based strategies for reducing cardiovascular risk, such as the management of blood pressure and lipid levels.

An audio version of this article is available at NEJM.org

Type 2 diabetes is preceded by a lengthy asymptomatic stage, termed prediabetes, which is characterized by mild hyperglycemia, insulin resistance, and early decrements in insulin secretory capacity. Data from randomized trials show that progression to diabetes from this at-risk stage can be reduced through lifestyle modification.[5,6] The identification of persons with prediabetes, who are now estimated to number 79 million in the United States,[1] allows for the introduction of interventions to reduce risk.

STRATEGIES AND EVIDENCE

SCREENING FOR DIABETES

The American Diabetes Association (ADA)[7] and the Veterans Health Administration (VHA)[8] recommend diabetes screening beginning at 45 years of age; the ADA advises earlier screening in patients with risk factors (Table 1). In contrast, routine screening is not recommended by the U.S. Preventive Services Task Force (USPSTF),[9] given the absence of rigorous data to show that screening and early treatment improve outcomes; this group recommends screening only in asymptomatic adults with a sustained blood pressure greater than 135/80 mm Hg — mainly because of lower blood-pressure targets once the diagnosis of diabetes is established.

KEY CLINICAL POINTS

DIAGNOSIS OF DIABETES

- Early screening and diagnosis allow for the identification of at-risk persons (so that preventive measures, primarily lifestyle changes, may be undertaken) and those with early disease (so that treatment can be initiated).
- The diagnostic cutoff point for diabetes is a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) or more or a glycated hemoglobin level of 6.5% or more; the diagnosis requires confirmation by the same or the other test.
- A fasting glucose level of 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter) is consistent with prediabetes; the range of glycated hemoglobin levels that are diagnostic of prediabetes is controversial, but the American Diabetes Association recommends a range of 5.7 to 6.4%.
- Hemoglobinopathies and conditions of altered red-cell turnover can give spurious results for glycated hemoglobin; racial and ethnic differences in glycated hemoglobin levels have been reported for given ambient glucose levels.
- Testing of glycated hemoglobin or fasting plasma glucose appears to identify different groups of patients with diabetes and prediabetes, yet both tests identify patients at similar risk for adverse sequelae.

DIAGNOSIS OF DIABETES

Glucose Levels

Before 1997, the diagnosis of diabetes was defined by the ADA and the World Health Organization (WHO) as a fasting plasma glucose level of 140 mg per deciliter (7.8 mmol per liter) or more or a 2-hour plasma glucose level of 200 mg per deciliter (11.1 mmol per liter) or more during an oral glucose-tolerance test (OGTT) conducted with a standard loading dose of 75 g. This definition was based on earlier recommendations from the National Diabetes Data Group.[10] These values were originally chosen on the basis of the risk of future symptoms of uncontrolled hyperglycemia. In 1997, with recommendations from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus,[11] the ADA and the WHO[12] lowered the diagnostic threshold to a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) — the level at which a unique microvascular complication of diabetes, retinopathy, becomes detectable. The OGTT identifies more patients as having diabetes than the fasting plasma glucose test, but the former test has drawbacks, including greater expense and complexity and lower reproducibility. Thus, the fasting plasma glucose test has been the preferred test in the United States. The diagnosis is confirmed by repeat testing on a separate day. In symptomatic patients, a random plasma glucose level of 200 mg per deciliter or more also establishes the diagnosis and does not require confirmation.

The only recognized at-risk category for diabetes before 1997 was impaired glucose tolerance, as identified on the basis of a 2-hour plasma glucose level of 140 to 199 mg per deciliter (7.8 to 11.0 mmol per liter) during an OGTT. With the revised 1997 criteria, a corresponding state was identified on the basis of the fasting plasma glucose level: impaired fasting glucose. Although the original criterion for this diagnosis was a fasting glucose level of 110 to 125 mg per deciliter (6.1 to 6.9 mmol per liter),[11] this criterion was later lowered by the ADA (but not by the WHO) to 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter) to increase sensitivity (with an acceptable drop in specificity) for persons with an increased diabetes risk.[13]

Longitudinal investigations have shown that persons categorized as being "impaired" by any of these definitions have approximately a 5 to 10% annualized risk of diabetes, a risk that is greater by a factor of approximately 5 to 10 than that among persons with normal glucose tolerance or normal fasting glucose. Risks appear to be similar among persons with isolated impaired fasting glucose (i.e., without impaired glucose tolerance) and isolated impaired glucose tolerance (without impaired fasting glucose).[14] However, the proportion of patients with impaired glucose tolerance tends to be greater than that with impaired fasting glucose in most populations. Persons with both impaired fasting glucose and impaired glucose tolerance have a higher risk of diabetes (approximately 10 to 15% per year) than those with only one abnormality. Whereas both prediabetic states are associated with increased total and cardiovascular mortality, impaired glucose

Table 1. American Diabetes Association Recommendations for the Screening of Asymptomatic Persons for Diabetes.*
Screen beginning at 45 yr of age, at least every 3 yr
Screen at any age and more frequently if the body-mass index is 25 or more and if the person has at least one additional risk factor:
Family history of diabetes (first-degree relative)
High-risk race (e.g., black, Native American, Asian, and Pacific Islander) or ethnic group (Hispanic)
Glycated hemoglobin level of 5.7% or more or impaired fasting glucose or impaired glucose tolerance on previous testing
History of gestational diabetes or delivery of a baby weighing more than 9 lb (4.1 kg)
The polycystic ovary syndrome
Hypertension (blood pressure ≥140/90 mm Hg; or therapy for hypertension)
HDL cholesterol level of less than 35 mg per deciliter (0.91 mmol per liter), triglyceride level of more than 250 mg per deciliter (2.8 mmol per liter), or both
History of cardiovascular disease
Physical inactivity
Other clinical conditions associated with insulin resistance (e.g., severe obesity and acanthosis nigricans)

* Data are adapted from the American Diabetes Association.[7] HDL denotes high-density lipoprotein.

tolerance tends to be a better predictor than impaired fasting glucose.[14]

Glycated Hemoglobin

Glycated hemoglobin has long been used in the management of established diabetes as a biomarker of long-term glycemic control. Levels of this end product of nonenzymatic glycation of the most prevalent protein in blood correlate well (though not perfectly) with average ambient blood glucose levels during the previous 2 to 3 months. Until recently, the lack of international standardization made glycated hemoglobin testing a suboptimal choice for diabetes screening. However, the glycated hemoglobin test is now globally standardized, so clinical laboratory results are comparable to those reported in the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study, two trials that validated the direct relationship between glycated hemoglobin levels and clinical outcomes in patients with type 1 and 2 diabetes, respectively.[15] In response, in 2009, the International Expert Committee (IEC) recommended the use of this test for the diagnosis of diabetes, with a threshold level of 6.5%.[16] This recommendation was based on the observation that the 6.5% threshold was as accurate in indicating a risk of retinopathy as were cutoff points for fasting plasma glucose and 2-hour plasma glucose, combined with the recognized advantages of glycated hemoglobin testing (Table 2), particularly the fact that fasting is not required. The measurement of glycated hemoglobin for diabetes diagnosis was subsequently adopted as an optional test by the ADA (in 2010)[18] and the WHO (in 2011).[19]

On the basis of data showing an increased risk of diabetes among persons with increased glycated hemoglobin levels that were still below the cutoff point for diabetes, the ADA also defined a prediabetic glycated hemoglobin range of 5.7 to 6.4%, which was an expansion of the original recommendation by the IEC that levels of 6.0% to 6.4% be considered high risk.[16,18] In contrast to the risk of retinopathy, which abruptly increases at a well-defined glycated hemoglobin level, the risk of diabetes increases along a glycemic continuum. As with fasting plasma glucose and 2-hour plasma glucose, the lower bound for such a range in glycated hemoglobin values must balance adequate sensitivity (to include persons who would benefit from prevention strategies) with specificity (to avoid the inclusion of persons at relatively low absolute risk, for whom intervention may not be cost-effective). The selected range described a group of persons with at least five times the risk of diabetes developing over a period of 5 to 10 years (and an annualized incidence of at least 5% per year) as compared with those with a glycated hemoglobin level of less than 5%. Logically, the risk increases further as a glycated hemoglobin level of 6.5% is approached, with a comparative relative

Table 2. Advantages and Disadvantages of Screening Tests for Diabetes.*

Testing Method	Advantages	Disadvantages
Fasting plasma glucose	Extensive experience, widespread availability, low cost	Fasting required, reflects glycemia solely at moment of sampling, substantial biologic variability, potential influence of acute illness, sample instability in vial, lack of global standardization
Oral glucose-tolerance test	Most sensitive test, earliest marker of glucose dysregulation	Fasting required, substantial biologic variability, poor reproducibility from day to day, lack of association of results with complications over time, sample instability in vial, more time required, inconvenience, higher cost, lack of global standardization of plasma glucose measurements
Glycated hemoglobin	Fasting not required, low biologic variability, marker of long-term glycemia, stable during acute illness, sample stability in vial, global standardization, close association of results with complications	Lack of reliability in patients with hemoglobinopathies (e.g., sickle cell disease and thalassemia, usually with reduced levels), unreliability in certain anemias with high red-cell turnover (e.g., hemolytic anemia, usually with reduced levels) or low red-cell turnover (e.g., iron deficiency, usually with increased levels), lack of reliability after recent transfusion (in the previous 2 to 3 mo), falsely low results in advanced (stage 4 or 5) renal disease, racial and ethnic differences (e.g., slightly higher in blacks), possibility of a glycation gap (differential glycation in response to the same ambient glucose exposure between persons), higher cost, lack of global availability

* Data are adapted from Sacks.[17]

risk in excess of a factor of 10 (and an annualized incidence of 5 to 10% per year).[20] The risk of diabetes at any given glycated hemoglobin level increases with the presence of other risk factors (e.g., obesity and a family history of diabetes).

Despite some advantages, the use of glycated hemoglobin testing has its limitations.[17] Depending on the assay, spuriously low values may occur in patients with certain hemoglobinopathies (e.g., sickle cell disease and thalassemia) or who have increased red-cell turnover (e.g., hemolytic anemia and spherocytosis)[21] or stage 4 or 5 chronic kidney disease, especially if the patient is receiving erythropoietin.[22] In contrast, falsely high glycated hemoglobin levels have been reported in association with iron deficiency and other states of decreased red-cell turnover.[23] Some investigators have reported a "glycation gap," or different glycated hemoglobin levels in patients with the same mean ambient blood glucose levels.[24] This phenomenon may result from genetically determined altered access of glucose to the intracellular compartment (where hemoglobin resides), although this hypothesis is controversial.[25] Inconsistencies in the correlations between glycated hemoglobin and other measures of ambient glycemia have also been reported in different ethnic and racial groups, findings that suggest genetic influences on hemoglobin glycation. For example, blacks appear to have slightly higher glycated hemoglobin levels (an absolute increase of 0.2 to 0.3 percentage points) than whites.[26] It is unclear whether this observation reflects differences in rates of postprandial hyperglycemia or in glycation rates.[27] These potential pitfalls must be recognized when glycated hemoglobin testing is used for diagnosis, especially for prediabetes, since the cutoff points for this state are already somewhat arbitrary.

In most studies, glycated hemoglobin testing identifies fewer patients with diabetes than does testing for fasting plasma glucose or 2-hour plasma glucose.[28-31] These measures may also identify distinct patients as having diabetes — groups that overlap only partially. For example, in a population-based study of U.S. adults without known diabetes, the proportions of patients with an abnormal fasting plasma glucose level (≥126 mg per deciliter) and a nondiabetic glycated hemoglobin level (<6.5%), a nondiabetic fasting plasma glucose level (<126 mg per deciliter) and an abnormal glycated hemoglobin level (≥6.5%), or both abnormalities were 1.8%, 0.5%, and 1.8%, respectively.[28] Moreover, in a prospective cohort study of older U.S. adults, roughly one third of cases of newly identified diabetes were detected by fasting plasma glucose testing only, one third by glycated hemoglobin testing only, and the remainder by both tests.[26] Furthermore, persons identified as having diabetes by glycated hemoglobin levels only were more likely to be black than those identified with the use of glucose levels.[26,28,29] Clearly, a move to increase the use of

glycated hemoglobin testing for screening would affect the epidemiology of diabetes.[32,33] Similar patterns have been reported for the diagnosis of prediabetes with glycated hemoglobin versus fasting plasma glucose.[29,32,33] Although these findings have led some observers to question the use of glycated hemoglobin for diagnostic purposes,[34,35] these questions are counterbalanced by the absence of an absolute standard measurement for the diagnosis of diabetes and the observation that all methods in use correlate equally well with retinopathy risk.[36]

Combined Screening

An alternative but more costly option, which has been proposed by several investigators,[37-40] is to measure both glycated hemoglobin and fasting plasma glucose, either simultaneously or in sequence, a strategy that might be considered for patients at highest risk. (In practice, fasting plasma glucose may have been checked as part of a routine blood chemical profile in patients who are being screened with glycated hemoglobin testing.) Given the different yields of these two measures, this approach is likely to capture substantially more patients than the use of either test in isolation.

When the results of two tests are available but discordant, a reasonable and cautious approach is to let the abnormal test result (if repeated and confirmed) guide categorization, as recommended by the ADA.[18] In this context, the nondiagnostic result usually is close to the abnormal range. However, if results are more widely discrepant (e.g., a fasting plasma glucose level of 123 mg per deciliter [6.8 mmol per liter] but a glycated hemoglobin level of 5.1%), repeat testing is indicated. In some cases, transient aberrations in glucose levels (as with acute illness) or abnormally low or high glycation rates may underlie such incongruities. An OGTT might be helpful in certain cases.

DIABETES PREVENTION

The identification of any prediabetic state warrants education of the patient regarding diabetes risk as well as lifestyle measures that may be undertaken to mitigate this risk. Two large clinical trials have shown the effectiveness of intensive lifestyle interventions in high-risk patients (overweight or obese with impaired glucose tolerance), with a relative risk reduction of 58% in the diagnosis of diabetes during a 3-year period.[5,6] The specific intervention in the largest study, the Diabetes Prevention Program (DPP), involved regular aerobic exercise (at least 30 minutes on most days of the week) and a calorie-restricted diet to promote the loss of 7% of body weight.[5] Metformin was also tested in the DPP; the relative risk reduction with this drug (31%) was approximately half that with lifestyle intervention, and the drug appeared to be particularly effective in patients under the age of 60 years, with a BMI over 35 and with a fasting plasma glucose level over 110 mg per deciliter.[5,41] Other glucose-lowering or antiobesity agents (i.e., acarbose, rosiglitazone, pioglitazone, and orlistat) have also been shown in randomized trials to reduce the risk of diabetes.[42] All drugs have important side effects to consider, and none are approved by the Food and Drug Administration (FDA) for this indication.

AREAS OF UNCERTAINTY

Although it appears logical to screen high-risk patients for dysglycemia, data are lacking to show that diabetes screening (outside of pregnancy) improves more than biochemical outcomes. The choice of a preferred screening test (fasting plasma glucose or glycated hemoglobin) remains arguable. In the United States, the OGTT has largely been abandoned outside of screening for gestational diabetes, owing to its complexity and low reproducibility.

It is unclear whether the risk of complications of diabetes differs according to whether the disease was diagnosed by means of fasting plasma glucose testing only or glycated hemoglobin testing only. Preliminary data from a large, community-based prospective cohort study suggest that the glycated hemoglobin level, which integrates fasting and postprandial glucose levels over a longer period, might be a better predictor of certain complications — especially cardiovascular disease.[43] It is also not known whether the risk of diabetes differs between patients identified as having prediabetes by means of glycated hemoglobin testing and those identified by means of fasting plasma glucose testing. Such risks probably vary according to which test is used ultimately to make the diagnosis. Ongoing research is assessing the value of risk scores that incorporate not only glycemic measures but also other biomarkers and risk factors to estimate diabetes risk.[44,45]

Other ambiguities relate to treatment strategies for patients in whom prediabetes has been

Table 3. **Major Diagnostic Criteria for Diabetes and Prediabetic or At-Risk States.***

Measure	American Diabetes Association		World Health Organization	
	Diabetes	Prediabetes	Diabetes	Impaired Glucose Regulation
Fasting plasma glucose	≥126 mg/dl	100–125 mg/dl (IFG)	≥126 mg/dl	110–125 mg/dl (IFG)
2-Hr plasma glucose (during an OGTT with a loading dose of 75 g)	≥200 mg/dl	140–199 mg/dl (IGT)	≥200 mg/dl	140–199 mg/dl (IGT)
Casual (or random) plasma glucose (in a patient with classic hyperglycemic symptoms)	≥200 mg/dl		≥200 mg/dl	
Glycated hemoglobin	≥6.5%	5.7–6.4%	≥6.5%	

* Data are adapted from the American Diabetes Association,[7,18] Alberti and Zimmet,[12] and the World Health Organization.[19] All listed plasma glucose levels are based on venous sampling. All tests (except for casual plasma glucose in a symptomatic patient) should be repeated and confirmed on a separate day. (The American Diabetes Association allows for glycated hemoglobin testing to be paired with fasting plasma glucose testing on the same day. If the values for both tests are in the diabetic range, the diagnosis is confirmed.) To convert the values for glucose to millimoles per liter, multiply by 0.05551. IFG denotes impaired fasting glucose, IGT impaired glucose tolerance, and OGTT oral glucose-tolerance test.

diagnosed. Do lifestyle or pharmacologic interventions in these patients truly prevent diabetes or simply delay its onset? Given the cumulative vascular risk associated with diabetes and the potential legacy effect of glycemic control (long-term benefit from early metabolic stability), even a modest delay of a few years in the onset of diabetes may be a worthwhile goal. However, diabetes-prevention trials to date[7,8] have focused on glycemic end points and were not powered to assess diabetes-related complications. Recent data suggest that generic metformin therapy may be particularly cost-effective in this context,[46] but the long-term benefits and risks of this or other medications (or bariatric surgery) are uncertain. There are also uncertain consequences of designating a risk factor (e.g., high fasting plasma glucose) as a disease state.

GUIDELINES

ADA[7,18] recommendations for diabetes screening are summarized in Table 1; the ADA diagnostic criteria are listed in Table 3, along with those of the WHO.[19] As mentioned, the USPSTF recommends screening only in adults with hypertension (blood pressure, >135/80 mm Hg).[9] The American Association of Clinical Endocrinologists (AACE),[47] the VHA,[8] and the WHO use the ADA criteria for diabetes; the AACE advises confirmation with fasting plasma glucose testing when the diagnosis is made on the basis of glycated hemoglobin testing. For the identification of prediabetes, the ADA is the sole group to fully endorse glycated hemoglobin testing, with a cutoff range of 5.7 to 6.4%[7,18] and no recommended confirmatory testing. The AACE allows for the use of glycated hemoglobin testing to screen for prediabetes but stipulates the need for follow-up testing of fasting plasma glucose for those with values of 5.5 to 6.4%.[47]

CONCLUSIONS AND RECOMMENDATIONS

The identification of patients with diabetes or prediabetes by screening allows for earlier intervention, with potential reductions in future complication rates, although randomized trials are lacking to definitively show benefit. The patient described in the vignette has risk factors (obesity, hypertension, and a family history of diabetes) and should be screened. Whether fasting plasma glucose or glycated hemoglobin is measured remains debatable; each test has advantages and disadvantages (Table 2). Given that the yield of testing is higher when both tests are performed, I typically assess both simultaneously — although most guidelines suggest the use of a single test initially. If the patient has positive results on both tests, the diagnosis is confirmed. If only one test is positive, I would repeat it on a separate day. If diabetes is confirmed, treatment should be initiated on the basis of current guidelines (see Fig. 1 for a proposed screening algorithm).[48,49]

If prediabetes is identified, a repeat test is not necessary. Lifestyle changes (diet and exercise) should be encouraged; a greater intensity of inter-

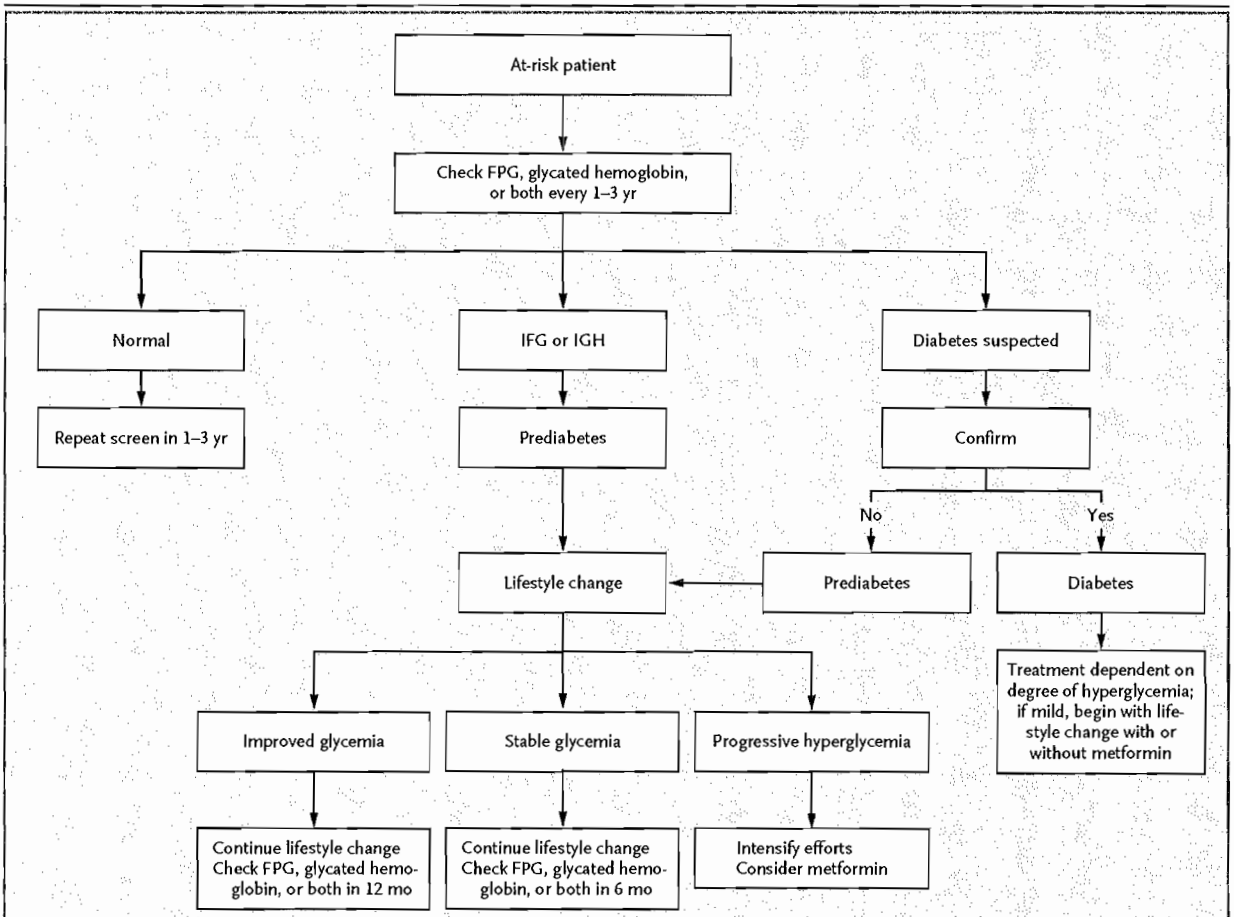


Figure 1. Suggested Approach to Screening Patients at Risk for Diabetes.

Impaired fasting glucose (IFG) is defined as a fasting plasma glucose (FPG) level of 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter). Increased glycated hemoglobin (IGH) is defined as a glycated hemoglobin level of 5.7 to 6.4%. The diagnosis of diabetes is confirmed with a repeat test on a separate day or by the alternative test (i.e., glycated hemoglobin instead of FPG or vice versa) on the same day or a separate day. If the result of the repeat test is in the prediabetic range, the patient should be counseled or treated for prediabetes. If the result of the repeat test is entirely normal (which is unlikely), rescreening in 6 months should be considered. Therapeutic lifestyle change is defined as a hypocaloric diet, weight reduction, and increased physical activity.

vention may be warranted in patients with higher glucose or glycated hemoglobin levels and with additional risk factors, since such findings predict more rapid progression to diabetes. I might consider metformin if progressive increases in glycemic measures were observed during follow-up, although the FDA has not approved metformin for this indication. Attention should also be paid to other cardiovascular risk factors. I might change the patient's antihypertensive therapy to an angiotensin-converting–enzyme inhibitor, given the associations between the use of a beta-blocker or thiazide and an increased risk of diabetes in some studies.[50] Periodic visits (every 6 to 12 months) are warranted to assess and encourage adherence to lifestyle recommendations and to follow glycemic status.

Dr. Inzucchi reports receiving consulting fees from Merck, Takeda Pharmaceuticals, Amylin Pharmaceuticals, Daiichi Sankyo, Boehringer Ingelheim, Medtronic, Purdue Pharma, Eisai, and Novartis; lecture fees from Novo Nordisk; payment for providing expert testimony on behalf of Eli Lilly regarding product litigation; and grant support to his institution from Takeda Pharmaceuticals, Merck, Amylin Pharmaceuticals, Eli Lilly, Medtronic, Boehringer Ingelheim, Abbott, and Novo Nordisk. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Dr. Kasia Lipska for her input during the preparation of an earlier version of this manuscript.

REFERENCES

1. Centers for Disease Control and Prevention. 2011 national diabetes fact sheet (http://www.cdc.gov/diabetes/pubs/factsheet11.htm).
2. United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53. [Erratum, Lancet 1999;354:602.]
3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
4. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Glucose control and cardiovascular disease in type-2 diabetes. Ann Intern Med 2009;151:394-403.
5. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
6. Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-50.
7. American Diabetes Association. Standards of medical care in diabetes — 2012. Diabetes Care 2012;35:Suppl 1:S11-S63.
8. Department of Veterans Affairs/Department of Defense. Management of diabetes mellitus in primary care (2010) (http://www.healthquality.va.gov/diabetes_mellitus.asp).
9. U.S. Preventive Services Task Force. Screening for Type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;148:846-55. [Erratum, Ann Intern Med 2008;149:147.]
10. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039-57.
11. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.
12. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. 1. Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
13. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160-7.
14. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabet Med 2002;19:708-23.
15. Hanas R, John G, International HBA1c Consensus Committee. 2010 Consensus statement on the worldwide standardization of the hemoglobin A1C measurement. Diabetes Care 2010;33:1903-4.
16. Nathan DM, Balkau B, Bonora E, et al. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327-34.
17. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care 2011;34:518-23.
18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33:Suppl 1:S62-S69. [Erratum, Diabetes Care 2010;33(4):e57.]
19. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation (http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/index.html).
20. Zhang X, Gregg EW, Williamson DF, et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care 2010;33:1665-73.
21. Sacks DB. Hemoglobin variants and hemoglobin A1c analysis: problem solved? Clin Chem 2003;49:1245-7.
22. Freedman BI, Shihabi ZK, Andries L, et al. Relationship between assays of glycemia in diabetic subjects with advanced chronic kidney disease. Am J Nephrol 2010;31:375-9.
23. Coban E, Ozdogan M, Timuragaoglu A. Effect of iron deficiency anemia on the levels of hemoglobin A1c in nondiabetic patients. Acta Haematol 2004;112:126-8.
24. Khera PK, Joiner CH, Carruthers A, et al. Evidence for interindividual heterogeneity in the glucose gradient across the human red blood cell membrane and its relationship to hemoglobin glycation. Diabetes 2008;57:2445-52.
25. Sacks DB, Nathan DM, Lachin JM. Gaps in the glycation gap hypothesis. Clin Chem 2011;57:150-2.
26. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. Ann Intern Med 2010;152:770-7.
27. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Ann Intern Med 2011;154:303-9.
28. Carson AP, Reynolds K, Fonseca VA, Muntner P. Comparison of A1C and fasting glucose criteria to diagnose diabetes among U.S. adults. Diabetes Care 2010;33:95-7.
29. Lipska KJ, De Rekeneire N, Van Ness PH, et al. Identifying dysglycemic states in older adults: implications of the emerging use of hemoglobin A1c. J Clin Endocrinol Metab 2010;95:5289-95.
30. Jørgensen ME, Bjerregaard P, Borch-Johnsen K, Witte D. New diagnostic criteria for diabetes: is the change from glucose to HbA1c possible in all populations? J Clin Endocrinol Metab 2010;95(1):E333-E336.
31. Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG, Phillips LS. Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. Diabetes Care 2010;33:2184-9.
32. James C, Bullard KM, Rolka DB, et al. Implications of alternative definitions of prediabetes for prevalence in U.S. adults. Diabetes Care 2011;34:387-91.
33. Mann DM, Carson AP, Shimbo D, Fonseca V, Fox CS, Muntner P. Impact of A1C screening criterion on the diagnosis of pre-diabetes among U.S. adults. Diabetes Care 2010;33:2190-5.
34. Bloomgarden ZT, Einhorn D. Hemoglobin A1c in diabetes diagnosis: time for caution. Endocr Pract 2010;16:5-6.
35. Cohen RM, Haggerty S, Herman WH. HbA1c for the diagnosis of diabetes and prediabetes: is it time for a mid-course correction? J Clin Endocrinol Metab 2010;95:5203-6.
36. Davidson MB. Diagnosing diabetes with glucose criteria: worshipping a false God. Diabetes Care 2011;34:524-6.
37. Hu Y, Liu W, Chen Y, et al. Combined use of fasting plasma glucose and glycated hemoglobin A1c in the screening of diabetes and impaired glucose tolerance. Acta Diabetol 2010;47:231-6.
38. Selvin E, Steffes MW, Gregg E, Brancati FL, Coresh J. Performance of A1C for the classification and prediction of diabetes. Diabetes Care 2011;34:84-9.
39. Fajans SS, Herman WH, Oral EA. Insufficient sensitivity of hemoglobin A1c determination in diagnosis or screening of early diabetic states. Metabolism 2011;60:86-91.
40. Heianza Y, Hara S, Arase Y, et al. HbA1c 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. Lancet 2011;378:147-55.
41. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753-9.
42. DeFronzo RA, Abdul-Ghani M. Type 2 diabetes can be prevented with early pharmacological intervention. Diabetes Care 2001;34:Suppl 2:S202-S209.
43. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800-11.
44. Kolberg JA, Jørgensen T, Gerwien RW, et al. Development of a type 2 diabetes

risk model from a panel of serum biomarkers from the Inter99 cohort. Diabetes Care 2009;32:1207-12.
45. Salomaa V, Havulinna A, Saarela O, et al. Thirty-one novel biomarkers as predictors for clinically incident diabetes. PLoS One 2010;5(4):e10100.
46. Herman WH. The economics of diabetes prevention. Med Clin North Am 2011;95:373-84.
47. American Association of Clinical Endocrinologists Board of Directors, American College of Endocrinologists Board of Trustees. American Association of Clinical Endocrinologists/American College of Endocrinology statement on the use of hemoglobin A1c for the diagnosis of diabetes. Endocr Pract 2010;16:155-6.
48. Ismail-Beigi F. Clinical practice. Glycemic management of type 2 diabetes mellitus. N Engl J Med 2012;366:1319-27.
49. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-79.
50. Taylor EN, Hu FB, Curhan GC. Antihypertensive medications and the risk of incident type 2 diabetes. Diabetes Care 2006;29:1065-70.

Screening for and clinical evaluation of obesity in adults

Author
George A Bray, MD

Section Editor
F Xavier Pi-Sunyer, MD, MPH

Deputy Editor
Jean E Mulder, MD

Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2014. | **This topic last updated:** Jan 30, 2013.

INTRODUCTION — Evaluation of an overweight patient should include both clinical and laboratory studies; the combined information is used to characterize the type and severity of obesity, determine health risk, and provide a basis for selecting therapy.

The approach to screening for and the clinical evaluation of obesity in adults will be reviewed here. The health risks associated with obesity and approach to treatment are discussed in detail separately. (See "Health hazards associated with obesity in adults" and "Overview of therapy for obesity in adults".)

MAGNITUDE OF THE PROBLEM — Obesity, a chronic disease that is increasing in prevalence in adults, adolescents, and children, is now considered to be a global epidemic. In most populations, the prevalence of overweight and obesity has increased over the past 20 years. In the United States, the lifetime risk of becoming overweight or obese is approximately 50 and 25 percent, respectively [1]. Health care expenditures are significantly higher for overweight and obese individuals. (See "Overview of therapy for obesity in adults", section on 'Prevalence' and "Health hazards associated with obesity in adults", section on 'Cost of obesity'.)

Rationale for screening — Obesity is associated with a significant increase in mortality (figure 1) and risk of many disorders, including diabetes mellitus, hypertension, dyslipidemia, heart disease, stroke, sleep apnea, cancer, and many others. Conversely, weight loss is associated with a reduction in obesity-associated morbidity.

For patients determined to be overweight or obese and at risk for obesity-associated disorders, a number of weight loss interventions are available including lifestyle, diet, exercise, pharmacotherapy, and surgery. (See "Overview of therapy for obesity in adults", section on 'Benefits of weight loss'.)

SCREENING — Screening for overweight and obesity should include measurement of body mass index (BMI), waist circumference, and evaluation of overall medical risk (figure 2). Subsequent intervention, if necessary, is then based upon overall risk assessment.

We suggest that all adult patients be screened for overweight and obesity by measuring BMI and waist circumference at the periodic health examination.

Unfortunately, screening for obesity does not yet appear to be a routine practice, as illustrated in a study of 9827 patients seen for general medical examinations during one year [2]. Of the 2543 obese patients, only 20 percent had a diagnosis of obesity or an obesity management plan made by their primary care clinician.

Measurement of BMI — Measuring body mass index (BMI) is the first step to determine the degree of adiposity. The BMI is easy to measure, reliable, and correlated with percentage of body fat and body fat mass. In addition, it is used for identifying adults at increased risk for morbidity and mortality due to obesity (table 1). The BMI can also be used to guide

selections of therapy (algorithm 1) [3].

There is evidence to support the use of BMI in risk assessment since it provides a better estimate of total body fat compared with body weight alone. Some think bioelectric impedance provides an advantage over BMI. Clinicians should be aware that BMI may overestimate the degree of obesity in individuals who are overweight but very muscular (for example, professional athletes or bodybuilders).

Calculating BMI — The distinction between overweight and obesity is made on the basis of the body mass index (BMI). The BMI is the most practical way to evaluate the degree of excess weight. It is calculated from the weight and square of the height as follows:

BMI = body weight (in kg) ÷ height (in meters) squared

The BMI can also be obtained from a table or a calculator (table 2A-B) (calculator 1).

Classification of BMI — The recommended classifications for BMI adopted by the National Institute of Health (NIH) and World Health Organization (WHO) [3,4] and endorsed by most expert groups are:

- Underweight — BMI <18.5 kg/m2
- Normal weight — BMI ≥18.5 to 24.9 kg/m2
- Overweight — BMI ≥25.0 to 29.9 kg/m2
- Obesity — BMI ≥30 kg/m2
- Obesity Class I — BMI of 30.0 to 34.9 kg/m2
- Obesity Class II — BMI of 35.0 to 39.9 kg/m2
- Obesity Class III — BMI ≥40 kg/m2. This type of obesity is also referred to as severe, extreme, or morbid obesity.

The relationship between BMI and risk allows identification of several levels that can be used to guide selection of therapy (algorithm 1) [4,5]. These arbitrary cutoffs are derived from data collected on whites. They have been widely adopted, but the definition of overweight and obesity varies by race. In some populations, the level of risk in terms of percent body fat is reached at a much lower BMI (South Asians) and in others a higher BMI (blacks) compared with whites (table 3) [6,7]. This was illustrated in a study comparing South Asian and European subjects. The mean BMI associated with development of an adverse metabolic profile (defined by markers of glucose and lipid metabolism) was 21 and 30 kg/m2 in South Asians and Europeans, respectively [7].

The current cutoffs underestimate risk in the Asian and South Asian population. Thus, the WHO and NIH Guidelines are currently applied to whites, Hispanics, and blacks (table 1). For Asians, overweight is a BMI between 23 and 24.9 kg/m2 and obesity a BMI >25 kg/m2 [8].

Waist circumference — Increasing central adiposity is associated with an increased risk of morbidity and mortality [9-12]. Therefore, in addition to measuring body mass index, waist circumference should be measured to assess abdominal obesity. Patients with abdominal obesity (also called central adiposity, visceral, android, or male-type obesity) are at increased risk for heart disease, diabetes, hypertension, and dyslipidemia. (See "Health hazards associated with obesity in adults".)

Although computed tomography (CT) and magnetic resonance imaging (MRI) are more accurate than waist circumference for assessing the distribution of body fat, they are too expensive to be performed for this purpose alone, except in research studies. Measurement of the waist-to-hip ratio provides no advantage over waist circumference

alone. (See "Determining body composition in adults".)

- The waist circumference is measured with a flexible tape placed on a horizontal plane at the level of the iliac crest as seen from the anterior view (figure 3).
- In adults with a BMI of 25 to 34.9 kg/m2, a waist circumference greater than 102 cm (40 in) for men and 88 cm (35 in) for women is associated with a greater risk of hypertension, type 2 diabetes, and dyslipidemia, and CHD (table 1) [13]. (See "Health hazards associated with obesity in adults", section on 'Coronary disease'.)
- In patients with a BMI ≥35 kg/m2, measurement of waist circumference is less helpful since it adds little to the predictive power of the disease risk classification of BMI; almost all individuals with this BMI also have an abnormal waist circumference [4].
- There is ethnic variability in waist circumference values that predict increased risk. As an example, Japanese-Americans and Indians from South Asia have more total fat and visceral fat and are therefore may be at higher risk of developing type 2 diabetes for a given BMI than whites [6,14]. In Asian females a waist circumference >80 cm and in Asian males a value >90 cm are considered abnormal.

Determine etiology — Most cases of obesity are related to nonmedical disorders such as a sedentary lifestyle and increased caloric intake. To determine etiology and plan future management strategies, additional medical history should include age at onset of weight gain, previous weight loss attempts, change in dietary patterns, history of exercise, current and past medications, and history of smoking cessation.

Medications are a common cause of weight gain and obesity, in particular insulin, sulfonylureas, thiazolidinediones, and antipsychotics. Smoking cessation is also associated with weight gain [15]. Although uncommon, some obese patients have an endocrine disorder such as Cushing's syndrome (table 4A-B). (See "Etiology and natural history of obesity".)

ASSESSMENT OF RISK STATUS — In patients with a BMI ≥25 kg/m2 or a waist circumference greater than 88 cm (women) or 102 cm (men), we suggest further evaluation of risk (algorithm 1). Assessment of an individual's overall risk status includes determining the degree of overweight (BMI), the presence of abdominal obesity (waist circumference), and the presence of cardiovascular risk factors or comorbidities (figure 2).

In addition to the medical history, blood pressure measurement, and lipid profile that are done routinely in adults, overweight or obese patients should have a fasting glucose measurement (figure 2).

Comorbidities — The coexistence of several diseases, including established CHD, other atherosclerotic disease, type 2 diabetes mellitus, and sleep apnea place patients in a very high-risk category for subsequent mortality. (See "Health hazards associated with obesity in adults", section on 'Mortality'.)

In addition to weight loss, these patients require aggressive modification of risk factors. (See "Overview of therapy for obesity in adults" and "Secondary prevention of cardiovascular disease".)

Obesity is also associated with other disorders that do not increase cardiovascular risk, but are associated with significant morbidity. Examples include osteoarthritis, cholelithiasis, and impaired quality of life. (See "Health hazards associated with obesity in adults".)

Cardiovascular risk factors — Other cardiovascular risk factors that contribute to risk should be identified, including hypertension, dyslipidemia (low HDL or high LDL), impaired fasting glucose, family history of premature CHD, age (≥45 for men, ≥55 for women), and cigarette smoking [4]. Physical inactivity also affects risk in obese patients.

Other factors — In addition to BMI, waist circumference, and the presence of comorbidities, cardiovascular risk factors and several additional factors may affect an individual's risk of morbidity and mortality associated with obesity:

- Pregnancy — Women have more fat as a percent of body weight than men from puberty onward, and tend to gain more fat during adult life than men. In addition, women experience modest but adverse increases in body weight and fat distribution after a first pregnancy that appear to persist. (See "Overview of postpartum care", section on 'Postpartum weight retention'.)

- Age of onset — The age of onset of obesity is of some importance in determining risk. Children with a low birth weight and those whose weight rises more rapidly in the first 10 years are at high risk for diabetes as adults [16]. The risk for any given degree of obesity seems to be greater in patients whose obesity begins before the age of 40, probably because of the longer time period over which comorbid conditions, such as diabetes mellitus and hypertension, can develop [17]. (See "Small for gestational age infant".)

- Weight gain after age 18 — Even very modest weight gain (≥5 kg) after age 18 years in women and after age 20 years in men increases the risk of CHD and type 2 diabetes at all levels of initial BMI [18]. (See "Health hazards associated with obesity in adults".)

EFFECTIVENESS OF SCREENING — There are no randomized trials comparing screening for obesity in adults with no screening. However, there are no known risks of screening for obesity and, therefore, the benefits of screening appear to outweigh the potential risks.

Evidence supporting screening — There are a number of arguments to support widespread screening for overweight and obesity:

- It is a common disease with significant morbidity and mortality and without screening many high risk patients may not receive counseling about health risks, lifestyle changes, obesity treatment options, and risk factor reduction.

- Screening with BMI, waist circumference, and risk factor assessment is inexpensive and available to nearly all clinicians.

- Weight loss is associated with a reduction in obesity-associated morbidity. (See "Overview of therapy for obesity in adults", section on 'Benefits of weight loss'.)

- A number of effective interventions are available for the management of obesity, including lifestyle interventions, pharmacotherapy, and surgery. (See "Overview of therapy for obesity in adults".)

Arguments against screening — Although there are no known risks associated with screening, a potential risk is the stigma of an obesity diagnosis. In addition, pharmacologic and surgical management of obesity have associated risk, and lifestyle changes are often ineffective. (See "Drug therapy of obesity" and "Bariatric operations for management of obesity: Indications and preoperative preparation".)

SCREENING RECOMMENDATIONS FROM EXPERT GROUPS — Guidelines for the screening and evaluation of overweight and obesity have been published by a number of organizations including the National Heart Lung and Blood Institute (NHLBI), The World Health Organization (WHO), and the US Preventive Services Task Force [3,5,19-22].

- The NIH recommends screening adults for obesity with BMI and waist circumference, and risk factor assessment. Subsequent intervention is then based upon overall risk assessment (algorithm 1) [5].

- The United States Preventive Services Task Force (USPSTF) recommends that "clinicians screen all adult patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese (BMI >30 kg/m2) adults" [22].

- The Canadian Task Force on Preventive Health Care recommends measuring BMI and waist circumference in all adults, but does not specify how often screening should be done [20].
- The American College of Obstetricians and Gynecologists recommend measuring BMI in all adult women [23].

We agree with the NIH guidelines and suggest that all adult patients be screened for overweight and obesity by measuring BMI and waist circumference at the periodic health examination.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Weight loss treatments (The Basics)")
- Beyond the Basics topics (see "Patient information: Weight loss treatments (Beyond the Basics)" and "Patient information: Weight loss surgery (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS — Evaluation of obese or overweight patients requires a comprehensive approach. Assessment of an individual's overall risk status includes determining the degree of overweight (BMI), the presence of abdominal obesity (waist circumference), and the presence of cardiovascular risk factors or comorbidities. We use an approach similar to those outlined by the National Institutes of Health and World Health Organization (see 'Screening recommendations from expert groups' above).

- We suggest that all adult patients be screened for overweight and obesity by measuring BMI and waist circumference at the periodic health examination (figure 3) (**Grade 2B**). Waist circumference measurement is unnecessary in patients with BMI ≥35 kg/m2. (See 'Screening' above.)
- In individuals with BMI ≥25 kg/m2 or a waist circumference greater than 88 cm (women) or 102 cm (men), we suggest further evaluation for cardiovascular risk factors and comorbidities (figure 2) (**Grade 2B**). (See 'Assessment of risk status' above.)

  The relationship between percent body fat and BMI is different among different ethnic groups. In some populations, the level of risk in terms of percent body fat is reached at a lower BMI (South Asians), and in others, a higher BMI (blacks), compared with whites (table 3). The WHO and NIH Guidelines are currently applied to whites, Hispanics, and blacks (table 1). For Asians, overweight is a BMI between 23 and 24.9 kg/m2 and obesity a BMI >25 kg/m2. (See 'Classification of BMI' above.)
- Subsequent interventions, including weight loss strategies and risk factor reduction, are then based upon overall risk assessment as outlined by the NHLBI and WHO (algorithm 1).
- Clinicians should counsel all overweight and obese patients on diet, lifestyle, and goals for weight loss. Specific recommendations for the treatment of obesity are reviewed separately. (See "Overview of therapy for obesity in adults" and "Drug therapy of obesity".)

REFERENCES

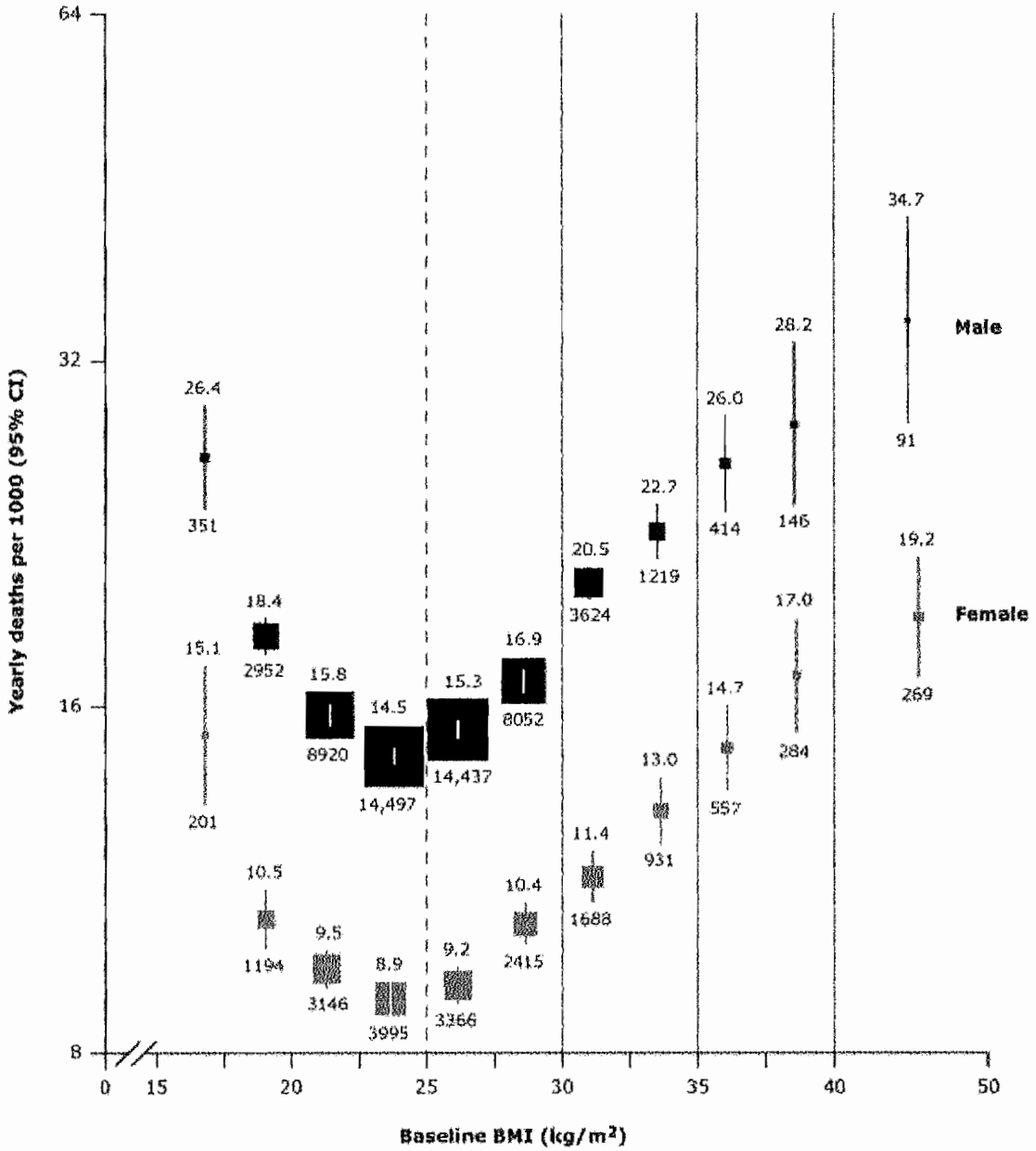
1. Vasan RS, Pencina MJ, Cobain M, et al. Estimated risks for developing obesity in the Framingham Heart Study. Ann Intern Med 2005; 143:473.
2. Bardia A, Holtan SG, Slezak JM, Thompson WG. Diagnosis of obesity by primary care physicians and impact on obesity management. Mayo Clin Proc 2007; 82:927.
3. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000; 894:i.
4. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998; 6 Suppl 2:51S.
5. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf (Accessed on January 23, 2013).
6. Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. Int J Obes Relat Metab Disord 1998; 22:1164.
7. Razak F, Anand SS, Shannon H, et al. Defining obesity cut points in a multiethnic population. Circulation 2007; 115:2111.
8. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363:157.
9. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr 2004; 79:379.
10. Simpson JA, MacInnis RJ, Peeters A, et al. A comparison of adiposity measures as predictors of all-cause mortality: the Melbourne Collaborative Cohort Study. Obesity (Silver Spring) 2007; 15:994.
11. Koster A, Leitzmann MF, Schatzkin A, et al. Waist circumference and mortality. Am J Epidemiol 2008; 167:1465.
12. Jacobs EJ, Newton CC, Wang Y, et al. Waist circumference and all-cause mortality in a large US cohort. Arch Intern Med 2010; 170:1293.
13. Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Arch Intern Med 2002; 162:2074.
14. Gallagher D, Heymsfield SB, Heo M, et al. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 2000; 72:694.
15. Filozof C, Fernández Pinilla MC, Fernández-Cruz A. Smoking cessation and weight gain. Obes Rev 2004; 5:95.
16. Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004; 350:865.
17. Fontaine KR, Redden DT, Wang C, et al. Years of life lost due to obesity. JAMA 2003; 289:187.
18. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999; 341:427.
19. Cornier MA, Després JP, Davis N, et al. Assessing adiposity: a scientific statement from the American Heart Association. Circulation 2011; 124:1996.
20. Lau DC, Obesity Canada Clinical Practice Guidelines Steering Committee and Expert Panel. Synopsis of the 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. CMAJ 2007; 176:1103.
21. Lyznicki JM, Young DC, Riggs JA, et al. Obesity: assessment and management in primary care. Am Fam Physician 2001; 63:2185.
22. Moyer VA, U.S. Preventive Services Task Force. Screening for and management of obesity in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012; 157:373.

23. ACOG Committee on Gynecologic Practice. ACOG committee opinion. Number 319, October 2005. The role of obstetrician-gynecologist in the assessment and management of obesity. Obstet Gynecol 2005; 106:895.

Topic 5372 Version 8.0

GRAPHICS

All-cause mortality versus BMI for each sex in the range 15 to 50 kg/m^2 (excluding the first five years of follow-up)



Relative risks at age 35 to 89 years, adjusted for age at risk, smoking, and study, were multiplied by a common factor (ie, floated) to make the weighted average match the PSC mortality rate at ages 35 to 79 years. Floated mortality rates shown above each square

and numbers of deaths below. Area of square is inversely proportional to the variance of the log risk. Boundaries of BMI groups are indicated by tick marks. 95% CIs for floated rates reflect uncertainty in the log risk for each single rate. Dotted vertical line indicates 25 kg/m^2 (boundary between upper and lower BMI ranges in this report). Above 25 kg/m^2, mortality was on average approximately 30 percent higher for every 5 kg/m^2 higher BMI.

BMI: body mass index; PSC: Prospective Studies Collaboration.

Graphic 73156 Version 4.0

Clinical and laboratory data for the evaluation of overweight patients

Height, in or cm	_____
Weight, lb or kg	_____
Calculated BMI, kg/m2	_____
Waist circumference, in or cm	_____
Blood pressure SBP/DBP, mm Hg	_____
Fasting serum triglyceride, mg/dL or mmol/L	_____
Serum Hdl-cholesterol, mg/dL or mmol/L	_____
Fasting blood glucose, mg/dL	_____
Are there symptoms of sleep apnea?	_____
Are there medication(s) that increase body weight?	_____
Is there regular physical activity?	_____
Are there other etiologic factors?	_____

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Graphic 69717 Version 3.0

Classification of overweight and obesity by BMI, waist circumference, and associated disease risk

	BMI kg/m^2	Obesity class	Disease risk* relative to normal weight and waist circumference	
			Men ≤102 cm (≤40 in)	>102 cm (>40 in)
			Women ≤88 cm (≤35 in)	>88 cm (>35 in)
Underweight	<18.5		-	-
Normal•	18.5 to 24.9		-	-
Overweight	25.0 to 29.9		Increased	High
Obesity	30.0 to 34.9	I	High	Very high
	35.0 to 39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

BMI: body mass index.

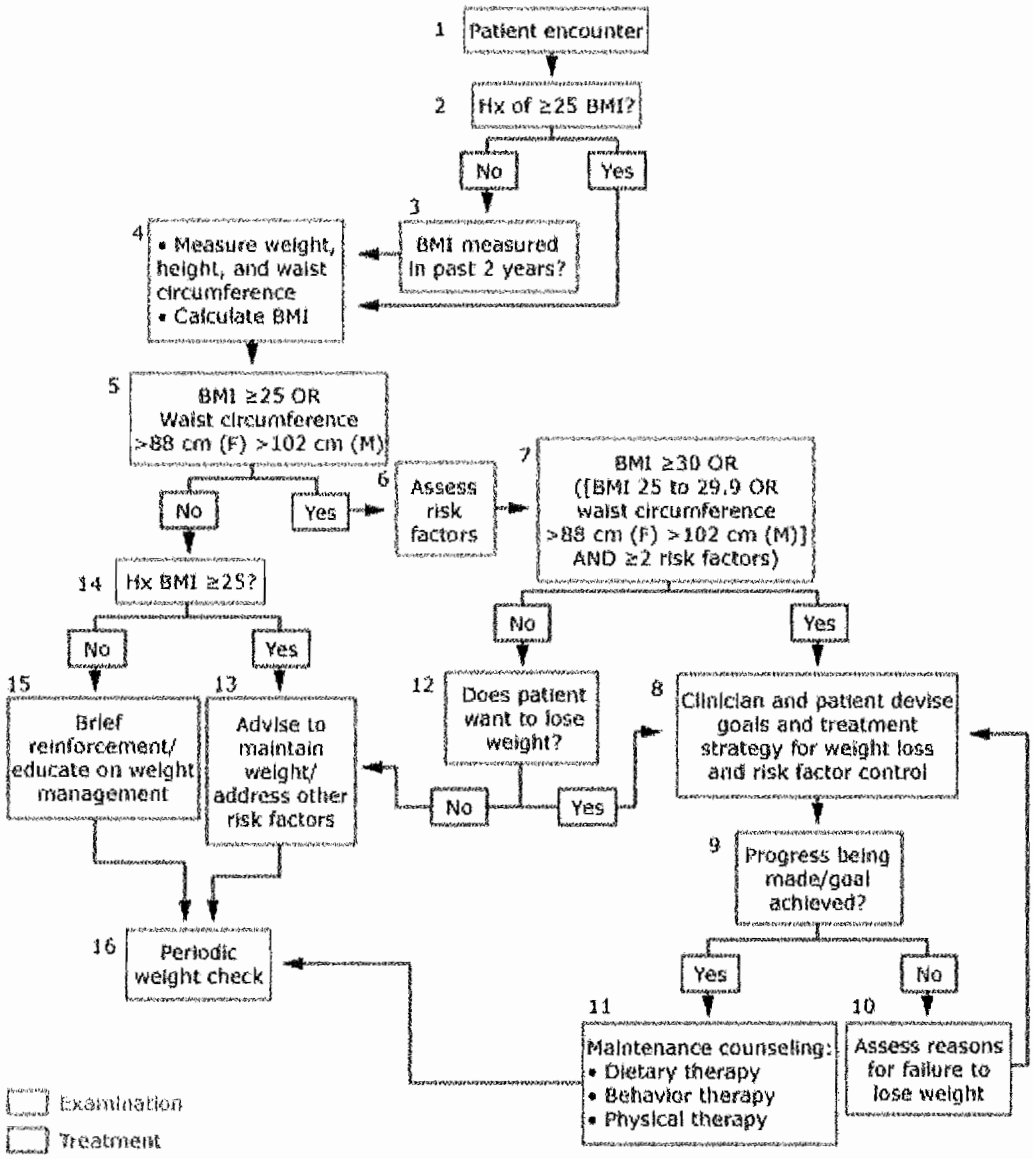
* Disease risk for type 2 diabetes, hypertension, and cardiovascular disease (CVD).

• Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Reproduced from: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998; 6:515.

Graphic 70466 Version 4.0

Treatment overweight and obesity algorithm*



Hx: history; BMI: body mass index; F: female; M: male.

* This algorithm applies only to the assessment for overweight and obesity and subsequent decisions based on that assessment. It does not include any initial overall assessment for cardiovascular risk factors or diseases that are indicated.

Reproduced from: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998; 6:51S.

Graphic 64983 Version 4.0

Determining body mass index from weight and height

	Good weights							Overweight					Obesity	
BMI, kg/m^2	19	20	21	22	23	24	25	26	27	28	29	30	35	40
Height, inches*	**Weight, pounds***													
58"	91	96	100	105	110	115	119	124	129	134	138	143	167	191
59"	94	99	104	109	114	119	124	128	133	138	143	148	173	198
60"	97	102	107	112	118	123	128	133	138	143	148	153	179	204
61"	100	106	111	116	122	127	132	137	143	148	153	158	185	211
62"	104	109	115	120	126	131	136	142	147	153	158	164	191	218
63"	107	113	118	124	130	135	141	146	152	158	163	169	197	225
64"	110	116	122	128	134	140	145	151	157	163	168	174	204	232
65"	114	120	126	132	138	144	150	156	162	168	174	180	210	240
66"	118	124	130	136	142	148	155	161	167	173	179	186	216	247
67"	121	127	134	140	146	153	159	166	172	178	185	191	223	255
68"	125	131	138	144	151	158	164	171	177	184	190	197	230	262
69"	128	135	142	149	155	162	169	176	182	189	196	203	236	270
70"	132	139	146	153	160	167	174	181	188	195	202	209	243	278
71"	136	143	150	157	165	172	179	186	193	200	208	215	250	286
72"	140	147	154	162	169	177	184	191	199	206	213	221	258	294
73"	144	151	159	166	174	182	189	197	204	212	219	227	265	302
74"	148	155	163	171	179	186	194	202	210	218	225	233	272	311
75"	152	160	168	176	184	192	200	208	216	224	232	240	279	319
76"	156	164	172	180	189	197	205	213	221	230	238	246	287	328

The health risk from any level of BMI is increased if the patient has gained more than 5 kg (11 pounds) since age 25, or if the waist circumference is above 100 cm (40 in) due to central fatness.

BMI: body mass index.

* Divide weight by 2.2 to convert pounds into kilograms; multiply height by 2.54 to convert inches into centimeters.

Graphic 63600 Version 2.0

Determining body mass index using kilograms and centimeters*

BMI, kg/m^2	19	20	21	22	23	24	25	26	27	28	29	30	35	40
Height, cm*	**Weight, kg***													
147	41	43	45	48	50	52	54	56	58	61	63	65	76	86
150	43	35	47	50	52	54	56	59	61	63	65	68	79	90
152	44	46	49	51	53	55	58	60	62	65	67	69	81	92
155	46	48	50	53	55	58	60	62	65	67	70	72	84	96
158	47	50	52	55	57	60	62	65	67	70	72	75	87	100
160	49	51	54	56	59	61	64	67	69	72	74	77	90	102
162	50	52	55	58	60	63	66	68	71	73	76	79	92	105
165	52	54	57	60	63	65	68	71	74	76	79	82	95	109
168	54	56	59	62	65	68	71	73	76	79	82	85	99	113
170	55	58	61	64	66	69	72	75	78	81	84	87	101	116
173	57	60	63	66	69	72	75	78	81	84	87	90	105	120
175	58	61	64	67	70	74	77	80	83	86	89	92	107	123
178	60	63	67	70	73	76	79	82	86	89	92	95	111	127
180	62	65	68	71	75	78	81	84	87	91	94	97	113	134
183	64	67	70	74	77	80	84	87	90	94	97	100	117	134
185	65	68	72	75	79	82	86	89	92	96	99	103	120	137
188	67	71	74	78	81	85	88	92	95	99	102	106	124	141
190	69	72	76	79	83	87	90	94	97	101	105	108	126	144
193	71	74	78	82	86	89	93	97	101	104	108	112	130	149

BMI: body mass index.

* The health risk from any level of BMI is increased if the patient has gained more than 5 kg (11 pounds) since age 25, or if the waist circumference is above 100 cm (40 in) due to central fatness.

Graphic 74762 Version 2.0

Variations in percent body fat for Caucasians, African-Americans, and Asians

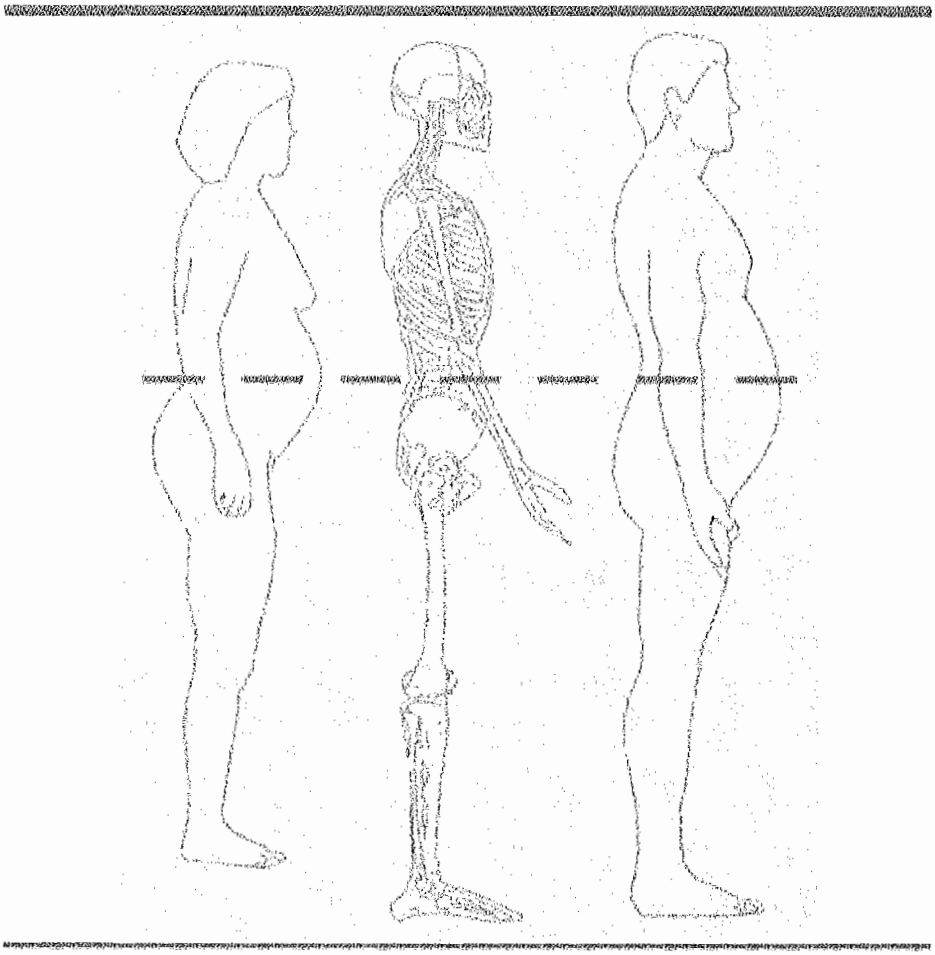
BMI (age)	Females			Males		
	African-American	Asian	Caucasian	African-American	Asian	Caucasian
Age 20 to 39	**Percent fat**					
18.5	20%	25%	21%	8%	13%	8%
25	32%	35%	33%	20%	23%	21%
30	38%	40%	39%	26%	28%	26%
Age 40 to 59	**Percent fat**					
18.5	21%	25%	23%	9%	13%	11%
25	34%	36%	35%	22%	24%	23%
30	39%	41%	41%	27%	29%	29%

BMI: body mass index; %: percent.

Data from: Gallagher D, Heymsfield SB, Heo M, et al. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 2000; 72:694.

Graphic 62675 Version 4.0

Waist circumference measurement



Measuring-tape position for waist (abdominal) circumference in adults. To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration.

Reproduced from: National Heart, Lung, and Blood Institute. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart Lung and Blood Institute, Bethesda, MD, October 2000.

Graphic 77584 Version 1.0

Etiologic classification of obesity

Iatrogenic causes
Drugs that cause weight gain
Hypothalamic surgery
Dietary obesity
Infant feeding practices
Progressive hyperplastic obesity
Frequency of eating
High fat diets
Overeating
Neuroendocrine obesities
Hypothalamic obesity
Seasonal affective disorder
Cushing's syndrome
Polycystic ovary syndrome
Hypogonadism
Growth hormone deficiency
Pseudohypoparathyroidism
Social and behavioral factors
Socioeconomic status
Ethnicity
Psychological factors
Restrained eaters
Night eating syndrome
Binge-eating
Sedentary lifestyle
Enforced inactivity (post-operative)
Aging
Genetic (dysmorphic) obesities
Autosomal recessive traits
Autosomal dominant traits
X-linked traits

Chromosomal abnormalities
Other
Low birth weight

Graphic 55594 Version 3.0

Drugs that cause weight gain and some alternatives

Category	Drugs that cause weight gain	Possible alternatives
Antipsychotics		
Conventional	Thioridazine	Haloperidol
Atypical	Olanzapine, Clozapine, Quetiapine, Risperidone	Ziprasodone, Aripiprazole
Lithium	Lithium carbonate	
Anti-depressants		
Tricyclics	Amitriptyline, Clomipramine, Doxepin, Imipramine, Nortriptyline	Protriptyline
Selective serotonin reuptake inhibitors	Paroxetine	Other SSRIs
Other	Mirtazapine	Bupropion, Nefazadone
Anticonvulsant drugs	Valproate, Carbamazepine, Gabapentin	Topiramate, Lamotrigine, Zonisamide
Antidiabetic drugs	Insulin, Sulfonylureas, Metiglinide, Thiazolidinediones	Metformin, Alpha-glucosidase inhibitors
Serotonin and histamine antagonist	Pizotifen	
Antihistamines	Cyproheptidine	
Beta-adrenergic blockers	Propranolol, Atenolol, Metoprolol	
Steroid hormones	Glucocorticoids	
	Progestins: Megestrol acetate, Medroxyprogesterone acetate	

SSRI: selective serotonin reuptake inhibitor.

Graphic 57541 Version 3.0

What is goal blood pressure in the treatment of hypertension?

Authors
Johannes FE Mann, MD
Karl F Hilgers, MD

Section Editors
George L Bakris, MD
Norman M Kaplan, MD

Deputy Editor
John P Forman, MD, MSc

Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2014. | **This topic last updated:** Jan 21, 2014.

INTRODUCTION — Systolic pressure generally rises with increasing age, while diastolic pressure reaches its peak in the fifth decade and subsequently falls [1]. These features are a reflection of the slow decrease in the compliance of the large capacitance vessels.

The net effect is that the risk from hypertension varies in part with age:

- Among untreated patients less than 65 years old, there is a progressive increase in the risk of stroke and coronary disease with increasing blood pressure. The risk is greater for each increment in systolic pressure than for the equivalent increase in diastolic pressure [2].
- For individuals over age 65 years, the risk continues to increase with the rising systolic pressure. However, a reversal occurs with the diastolic pressure: the lower the diastolic pressure at a given systolic pressure, the greater the risk [3]. Thus, an increased pulse pressure is associated with an increased risk of an adverse event.

The relative prognostic importance of the different blood pressure components in individuals of different ages was perhaps best studied among participants in the Second National Health and Nutrition Examination Survey (NHANES II) [4]. In this cohort study of 7830 participants between the ages of 30 to 74 years who were initially free of cardiovascular disease, the baseline blood pressure was correlated with all-cause and cardiovascular mortality over a 15 year follow-up. Over this period, 1588 patients died, with cardiovascular disease being responsible in 582 (37 percent).

Unlike previous studies, the analysis was based upon a generalized additive risk model that utilized the correlation between systolic and diastolic blood pressures to estimate the risk for different baseline blood pressure combinations. As a result, the risk associated with a blood pressure of 150/100 mmHg could be ascertained, whereas other studies permitted determination of the risk of a systolic pressure of 150 mmHg or a diastolic pressure of 100 mmHg, but not the combination [5]. In the latter studies, the risk attributed to a diastolic pressure of 100 mmHg was a composite of the range of systolic pressures associated with this diastolic pressure.

The following results were obtained concerning mortality beyond the first two years of follow-up:

- Among participants less than 65 years of age, increases in the systolic blood pressure were linearly related to increases in cardiovascular and all-cause mortality at **all** diastolic blood pressure levels. By comparison, the correlation between diastolic blood pressure and mortality in this age group was "hockey stick-shaped." This shape corresponds to a flat region of risk with diastolic values below 80 mmHg, with a marked increase in risk occurring with values above this level.
- Among those greater than 65 years of age, increases in the systolic pressure were also linearly related to

increased mortality at all diastolic pressures. However, the risk with the diastolic pressure was J-shaped; thus, for a fixed systolic pressure, increasing diastolic pressure that was below approximately 80 to 90 mmHg was associated with a decreased risk of mortality, while increasing diastolic pressure above 80 to 90 mmHg was associated with an enhanced risk.

- Increased pulse pressure was associated with marked variations in risk of mortality, depending upon age, and the exact systolic and diastolic pressure.

An increasing number of trials have provided evidence that antihypertensive therapy that results in adequate blood pressure control provides some degree of cardiovascular protection. However, the optimal level of control is unclear and may vary with certain patient populations [6,7]. In general, the benefits of increasingly intensive therapy must be weighed against the potentially increased incidence of serious side effects associated with such a regimen.

The rationale for specific goal blood pressure levels in the general hypertensive population and the possible risks of excessive blood pressure lowering will be reviewed here. The indications for antihypertensive therapy in mild hypertension, the choice of antihypertensive drugs for the initial treatment of hypertension, and goal blood pressure in patients with atherosclerotic cardiovascular disease, diabetes mellitus, and chronic kidney disease are presented separately. (See "Hypertension: Who should be treated?" and "Choice of therapy in primary (essential) hypertension: Recommendations" and "Blood pressure management in patients with atherosclerotic cardiovascular disease", section on 'Goal blood pressure' and "Treatment of hypertension in patients with diabetes mellitus", section on 'Goal blood pressure' and "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal'.)

SYSTOLIC AND DIASTOLIC HYPERTENSION — Systolic and diastolic hypertension in the general population are defined as a blood pressure ≥140/≥90 mmHg measured on at least three separate occasions. (See "Hypertension: Who should be treated?", section on 'Definitions'.)

Benefits of blood pressure reduction — Randomized controlled trials of antihypertensive therapy demonstrated significant cardiovascular benefit in patients with systolic and diastolic hypertension that was most pronounced in severe and moderate disease. Although the number of patients was small in the severe and moderate hypertension trials, the magnitude of benefit was extremely high.

Severe hypertension — The best data on the treatment of severe diastolic hypertension come from a trial of 143 men with diastolic pressures of 115 to 129 mmHg (average clinic blood pressure 186/121 mmHg) who were randomly assigned to antihypertensive therapy or placebo, the incidence of cardiovascular events was 3 percent at 21 months in the treated group versus 39 percent at 16 months in the placebo group ($p<0.001$) [8]. The shorter follow-up in the placebo group was due to the high number of terminating events. The average blood pressure during the trial was significantly lower in the treated group (143/91 mmHg versus no significant change in the placebo).

Moderate hypertension — The efficacy of treating moderate diastolic hypertension was demonstrated in a trial of 210 men with diastolic pressures of 105 to 114 mmHg who were randomly assigned to antihypertensive drugs or placebo, the incidence of cardiovascular events at five years was significantly lower in the treated group (8 versus 32 percent) [9].

Mild hypertension — The absolute benefit of blood pressure lowering is much lower in patients with mild hypertension (diastolic pressures of 90 to 104 mmHg). A summary of the results from 17 controlled trials of mild to moderate diastolic hypertension (almost all also had systolic hypertension) in adults under age 65 years found that active treatment with antihypertensive medications (which produced a mean reduction in diastolic pressure of 5 to 6 mmHg) led to a statistically significant 16 percent reduction in the number of coronary events and a 40 percent reduction in stroke [10]. In the aggregate, antihypertensive therapy for four to five years prevented a coronary event in 0.7 percent of patients and a cerebrovascular event in 1.3 percent for a total absolute benefit of approximately **2 percent**; this

included an absolute reduction in cardiovascular mortality of 0.8 percent (figure 1).

There are **no** randomized trials that have evaluated the efficacy of treating mild hypertension in patients with baseline systolic pressures of 140 to 149 mmHg. The three largest randomized trials that have been performed — the Medical Research Council (MRC) trial, the Hypertension Detection and Follow-up Program (HDFP), and the FEVER trial — included patients with mean baseline systolic pressures of 150 to 160 mmHg [11-14]. All showed significant benefit from antihypertensive therapy, which lowered the mean blood pressure to less than 140 mmHg systolic and/or less than 90 mmHg diastolic.

- MRC trial – In the MRC trial, 17,354 patients with a baseline diastolic pressure 90 to 109 mmHg were randomly assigned to bendrofluazide, propranolol, or placebo [11]. The mean baseline blood pressure was approximately 161/98 mmHg; the mean attained blood pressure was approximately 137/86 in the two treated groups and 150/92 in the placebo group. The treated groups had significantly lower rates of all cardiovascular events (6.7 versus 8.2 per 1000 patient years) and of stroke but not of coronary events or mortality.

- HDFP trial – In stratum I of the HDFP trial, 7825 patients with mild hypertension (diastolic pressure 90 to 104 mmHg) were randomly assigned to intensive therapy in special clinics (stepped care) or to usual source of care therapy in the community [12]. The main end point was total mortality at five years, which was significantly lower with stepped care (5.9 versus 7.4 percent, absolute benefit 1.5 percent, 95% CI 0.4-2.6 percent). The magnitude of benefit was similar but not quite significant for the almost 3000 patients with an entry diastolic pressure of 90 to 94 mmHg (absolute benefit 1.6 percent, 95% CI -0.2 to +3.4 percent) [13]. The average attained diastolic pressure was 85 and 90 mmHg in the stepped care; systolic pressures were not given.

- FEVER trial – The Felodipine Event Reduction (FEVER) trial included 9800 patients with previously treated hypertension who were switched from previous antihypertensive therapy to hydrochlorothiazide at a dose of 12.5 mg/day [14]. At six weeks after switching, the patients were randomly assigned to felodipine or placebo; the baseline blood pressure was 154/91 mmHg. Add-on therapy had to be given to 34 and 42 percent of patients, respectively. At a mean follow-up of 40 months, the average blood pressure was lower in the felodipine group (137/83 versus 143/85 mmHg with placebo). The primary endpoint of fatal and nonfatal stroke occurred in significantly fewer patients in the felodipine group (3.7 versus 5.2 percent); all-cause mortality was also reduced (2.3 versus 3.1 percent).

Blood pressure goal — In the aggregate, the above findings from the MRC, HDFP stratum I, and FEVER trials support the recommended goal blood pressure of <140/<90 mmHg in the general hypertensive population. However, supportive data for such a goal in patients with grade or stage 1 hypertension (systolic 140 to 159 mmHg and/or diastolic 90 to 99 mmHg) are limited [7]. Most trials, except for stratum I in HDFP, included patients whose blood pressure at baseline was higher than these values. (See "Hypertension: Who should be treated?", section on 'Definitions'.)

Blood pressure goals for patients with systolic and diastolic hypertension vary according to age and the presence of comorbid conditions:

- In the general hypertensive population of younger adults (ie, younger than 60 years of age), we agree with major societies and organizations that recommend a goal blood pressure of <140/<90 mmHg [6,7,15-17].

- In the general hypertensive population of older adults (ie, 60 years and older, nondiabetic, no chronic kidney disease), we recommend a goal blood pressure <150/<90 mmHg and, in patients aged 60 to 79 years, also suggest reducing systolic pressure to <140 mmHg if it can be achieved without producing significant side effects. These recommendations are consistent with most major societies and organizations [6,15-18], although members of the Eighth Joint National Committee (JNC 8) did not suggest lowering the systolic pressure below 140 mmHg [7]. In older patients with diabetes or chronic kidney disease, we recommend a blood pressure goal of <140/<90 mmHg, consistent with major societies and organizations.

- Lower goals are suggested for patients with certain comorbid conditions, such as those with atherosclerotic cardiovascular disease or in patients with proteinuric chronic kidney disease. (See 'Lower goal in patients at increased risk' below and "Blood pressure management in patients with atherosclerotic cardiovascular disease", section on 'Goal blood pressure' and "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal'.)

Related issues of whom to treat with antihypertensive therapy, and goal blood pressure in patients with isolated systolic hypertension, are discussed separately. (See "Hypertension: Who should be treated?", section on 'Systolic and diastolic hypertension' and "Treatment of hypertension in the elderly patient, particularly isolated systolic hypertension", section on 'Goal blood pressure'.)

Goal blood pressure versus achieved blood pressure — It is important to keep in mind that there is a meaningful difference between goal blood pressure and achieved blood pressure. Many trials have demonstrated that lower **achieved** blood pressure is associated with superior outcomes, while comparatively few trials have directly evaluated two different **goal** (ie, target) blood pressures.

J-shaped diastolic curve — There is conflicting evidence related to the possible risk of excessive reduction in the **diastolic** blood pressure. Rather than demonstrating a progressive benefit at lower pressures, many trials revealed a J-shaped curve in which the risk of cardiac events declines as the diastolic pressure falls from above 100 mmHg to 85 mmHg, but then rises back up at pressures below 80 to 85 mmHg [19,20]. By comparison, there is little evidence suggesting a J-curve for the **systolic** blood pressure, other than perhaps isolated systolic hypertension (see below).

The following sections will review some of the evidence suggesting that a J-shaped curve does (positive studies) or does not exist (negative studies) for the treatment of diastolic hypertension.

Positive studies — Several long-term reports in patients with diastolic hypertension have evaluated the incidence of cardiovascular complications according to the mean in-study diastolic blood pressure. As mentioned, an enhanced cardiovascular risk of cardiac events has been observed in some studies with diastolic pressures below 80 to 85 mmHg [4,19-24]. This was observed, for example, among individuals greater than 65 years of age who were participants in the NHANES II survey cited above [4]. For a fixed systolic pressure, decreased diastolic pressures below approximately 80 to 90 mmHg were associated with increasing mortality.

It is possible that patients with coronary disease do worse at these lower pressures because much of coronary perfusion occurs during diastole; alternatively, low diastolic blood pressures may be a reflection of underlying severe vascular disease, or other chronic illness. Observations from the Framingham study are compatible with the potential importance of underlying coronary disease; a J-shaped curve for coronary deaths was noted for patients who had a myocardial infarction but not for those who did not [21]. Similarly, in the Irbesartan Diabetic Nephropathy Trial, there was an increased risk for myocardial infarction, but a lower risk of stroke, with achieved diastolic blood pressures below 85 mmHg [22], as well as in people with vascular disease in the ONTARGET [25] and INVEST [26] trials.

A secondary analysis of the INVEST trial of over 22,000 patients demonstrated a strong J-shaped relationship between diastolic blood pressure and adverse outcomes (death, nonfatal myocardial infarction or nonfatal stroke) [23]. In this study, however, more patients with a mean follow-up diastolic blood pressure less than 70 mmHg had a history of myocardial infarction and heart failure than those with higher diastolic pressures (>40 versus <30 percent, and 10 versus 5 percent, respectively). The J-shaped relationship was markedly attenuated in multivariate analyses adjusted for myocardial infarction, heart failure, and risk factors for cardiovascular disease, suggesting that the J-shaped relationship is partly related to underlying coronary artery disease. (See 'Negative studies' below and "Choice of therapy in primary (essential) hypertension: Clinical trials", section on 'INVEST trial'.)

Two important factors must be considered from these observations. First, the increase in risk has been noted only at relatively low diastolic pressures, **below 70 to 75 mmHg**. Second, as will be described in the next section, randomized

trials with placebo control have shown a similar J-curve in both treated and placebo groups and for noncardiovascular as well as cardiovascular mortality (figure 2), suggesting that patients with lower diastolic pressures are at higher risk independent of antihypertensive therapy [27,28].

Negative studies — There are a number of studies that raise serious questions about the importance of the J-curve relating to diastolic blood pressure reduction with antihypertensive medications at usual levels of blood pressure control [27,29-33]:

- During the first two years of follow-up of over 5000 subjects with a history of a myocardial infarction, there was no detectable association between systolic blood pressure and coronary mortality [29]. Over the ensuing 14 years, however, linear associations were noted between the risk of coronary death and both systolic and diastolic pressure; patients with lower pressures were at lower risk.
- The Modification of Diet in Renal Disease study suggested that more aggressive blood pressure lowering (systolic pressure below 130 mmHg) slows the rate of progression of chronic renal disease in patients excreting more than 1 to 2 g of protein per day (figure 3) [30]. An incidental observation was a direct relation between the systolic and diastolic pressures and hospitalization for a first cardiovascular or cerebrovascular event. From the first (88 to 119 mmHg) to the fourth (>138 mmHg) quartiles of systolic pressure, the likelihood of such an event increased progressively from 0.4 to 2.2 to 2.9 to 5.8 percent per patient year of follow-up. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal'.)
- In a prospective evaluation of over 6000 patients for nine years, a J-curve did not appear except in patients with mild to moderate hypertension whose diastolic pressure was aggressively lowered by more than 25 mmHg from the baseline value [31].
- In the Systolic Hypertension in the Elderly Program (SHEP), treated older adult patients with isolated systolic hypertension (and an initial diastolic pressure averaging 77 mmHg) had a lower incidence of both cerebrovascular and coronary events despite a reduction of the diastolic pressure to below 70 mmHg [32].

The issue of the J-curve was also addressed in a meta-analysis that analyzed individual patient data from seven randomized trials of both diastolic and isolated systolic hypertension [27]. Although a J-curve was detected for mortality in relation to diastolic pressure, it was seen in both treated and untreated patients and was not specific for cardiovascular mortality (figure 2). The authors concluded that the J-curve is probably explained by poor health associated with lower blood pressures rather than an adverse effect of antihypertensive therapy.

In contrast, another meta-analysis of randomized, placebo controlled trials including more than 28,000 patients found that lowering blood pressure was beneficial even in individuals with diastolic blood pressure below 70 mmHg, **as long as the systolic blood pressure was lowered** [34].

HOT trial — The Hypertension Optimal Treatment (HOT) trial was designed to settle the controversy over whether the J-curve exists by comparing outcomes among patients randomized to three different **diastolic pressure** goals [35]. In this prospective study, almost 19,000 patients (average pretreatment blood pressure of 170/105 mmHg) were randomly assigned to target diastolic pressures of ≤90, ≤85, or ≤80 mmHg. Treatment was begun with the long-acting dihydropyridine calcium channel blocker felodipine (5 mg once a day). Either an ACE inhibitor or a beta-blocker was added if the target pressure was not obtained with initial therapy. Further therapeutic options included increasing the doses of these agents or adding a diuretic. After an average follow-up period of approximately four years, 78, 41, 28, and 22 percent of patients were taking felodipine, an ACE inhibitor, a beta-blocker, and a diuretic, respectively. The trial outcome was negative.

Two significant problems emerged that clouded the power of this study:

- Since the cardiovascular event rate was lower than had been anticipated, the study duration was prolonged.

- Less separation in the diastolic blood pressure was achieved among the three target groups than had been planned; the mean diastolic blood pressures attained for the ≤90, ≤85 mmHg, or ≤80 mmHg groups were 85, 83, and 81 mmHg, respectively. The respective mean systolic blood pressures were 144, 141, and 140 mmHg. This close degree of blood pressure reduction among the three groups fails to provide the power to detect any difference in protection with varying degrees of blood pressure lowering. The data therefore did not disprove or prove the existence of a J-curve.

An analysis of the correlation between adverse cardiovascular events and blood pressures achieved with antihypertensive therapy revealed that the fewest major events (figure 4A-B) and the lowest cardiovascular mortality (figure 5A-B) were noted at average blood pressures of 138/83 and 139/86 mmHg, respectively. Lower blood pressures were not associated with a further change in the number of adverse events, except for an apparent increase in mortality in those in whom the diastolic pressure was reduced to below 70 mmHg [36].

Subsequent subgroup analyses of the HOT trial found that smokers randomly assigned to the two lower diastolic blood pressure values, compared with those assigned to the less than 90 mmHg target, had significant increases in the risk of major cardiovascular events (RR 1.71), stroke (RR 2.44), cardiovascular death (RR 2.67), total death (RR 2.03), sudden death (RR 2.93), but not myocardial infarction [37]. Although this adverse effect may be due to chance, support for its validity includes the large number of smokers studied (nearly 3000 patients); smoking was included in the randomization; and no baseline differences in characteristics were noted among smokers in the three randomized categories. The possible reasons for this finding, if true, are unclear [37,38].

TREATMENT OF ISOLATED SYSTOLIC HYPERTENSION — Isolated systolic hypertension is considered to be present when the blood pressure is ≥140/<90 mmHg and isolated diastolic hypertension, which is discussed elsewhere, is considered to be present when the blood pressure is <140/≥90 mmHg. (See "Hypertension: Who should be treated?", section on 'Definitions' and "Hypertension: Who should be treated?", section on 'Isolated diastolic hypertension'.)

Benefit of blood pressure reduction — The benefit of blood pressure reduction in patients with isolated systolic hypertension was demonstrated in a meta-analysis that included eight outcome trials of 15,693 patients ≥60 years of age with isolated systolic hypertension (including SHEP, Syst-Eur, and MRC described below) [3]. At a median follow-up of 3.8 years, the number of patients who needed to be treated for five years to prevent one major cardiovascular event was lower in men (18 versus 38 in women), patients aged 70 years or more (19 versus 39 in patients under age 70 years), and those with previous cardiovascular complications (16 versus 37 without such a history).

Total mortality correlated directly with systolic blood pressure at study entry, but inversely with diastolic blood pressure. However, diastolic blood pressure was not significantly associated with outcome for combined fatal and nonfatal events. (See "Treatment of hypertension in the elderly patient, particularly isolated systolic hypertension".)

J-shaped systolic curve — Many of the above reports did not support a J-curve for the **systolic pressure** [1-5,19-23,27-31]. The risk of cardiovascular disease generally declines continuously at least down to a systolic pressure of 130 to 140 mmHg overall and down to a systolic pressure of 120 mmHg in certain patient populations, such patients with diabetes and/or chronic kidney disease. (See 'Lower goal in patients at increased risk' below.)

Some evidence, however, suggests that a J-curve exists for the development of stroke and other cardiovascular events among patients with isolated systolic hypertension in whom low-normal diastolic pressures are lowered further by antihypertensive therapy.

However, the question of how much the blood pressure should be lowered in older adult patients with isolated systolic hypertension is uncertain in view of evidence that adverse outcomes are seen with low diastolic blood pressures.

- In the Rotterdam Study involving 2351 older adult hypertensives, those who received antihypertensive therapy experienced a progressive decrease in the incidence of stroke as their diastolic blood pressure was lowered to the

65 to 74 mmHg range [39]. However, a significant increase in stroke was observed when the diastolic blood pressure was lowered to less than 65 mmHg.

- In a reanalysis of data from the Systolic Hypertension in the Elderly Program, those who experienced a cardiovascular event while on antihypertensive drug therapy had lower diastolic levels than those who did not have an event (65 versus 68 mmHg) [40,41]. Overall, a decrease of 5 mmHg in diastolic blood pressure (which initially averaged 77 mmHg) in treated patients was associated with statistically significant increases in all cardiovascular events and in stroke (14 and 11 percent, respectively), particularly at pressures ≤60 mmHg.

Three factors must be considered when interpreting these findings:

- Lower diastolic pressures may reflect less aortic compliance due to atherosclerosis, rather than excessive blood pressure reduction. If so, then lower diastolic pressures with therapy are a marker for not a cause of worse outcomes.
- The risk in patients with lower diastolic pressures was still less than in placebo-treated patients whose systolic pressures remained elevated.
- In the meta-analysis described above, which included two trials of isolated systolic hypertension, a J-curve for mortality in relation to systolic pressure was noted (figure 6) [27]. However, it was seen in both treated and untreated patients and was not specific for cardiovascular mortality. Similar findings were noted for diastolic pressure (figure 2). The authors concluded that the J-curve is probably explained by poor health associated with lower blood pressures rather than an adverse effect of antihypertensive therapy.

In summary, there is no clear evidence supporting a treatment-related J-curve in patients with isolated systolic hypertension. Nevertheless, careful monitoring is advised when treating older adult patients who start with low diastolic pressures [41]. (See "Treatment of hypertension in the elderly patient, particularly isolated systolic hypertension".)

GOAL BLOOD PRESSURE — The goal blood pressures presented below refer to the levels at which more intensive antihypertensive therapy to produce a further reduction in blood pressure is **not** recommended. These goals are broadly consistent with recommendations from major societies and organizations [6,7,15-17]:

- In the general hypertensive population of younger adults (ie, younger than 60 years of age), we agree with major societies and organizations that recommend a goal blood pressure of <140/<90 mmHg [6,7,15-17].
- In the general hypertensive population of older adults (ie, 60 years and older, nondiabetic, no chronic kidney disease), we recommend a goal blood pressure <150/<90 mmHg and, in patients aged 60 to 79 years, also suggest reducing systolic pressure to <140 mmHg if it can be achieved without producing significant side effects. These recommendations are consistent with most major societies and organizations [6,15-18], although members of the Eighth Joint National Committee (JNC 8) did not suggest lowering the systolic pressure below 140 mmHg [7]. In older patients with diabetes or chronic kidney disease, we recommend a blood pressure goal of <140/<90 mmHg, consistent with major societies and organizations.

  These systolic blood pressure targets also apply to older adults with isolated systolic hypertension. However, as described above, the diastolic blood pressure should be reduced to a minimum posttreatment diastolic pressure of >60 mmHg overall or perhaps >65 mmHg in patients with known coronary artery disease unless symptoms that could be attributable to hypoperfusion occur at higher pressures. In many cases, the level of systolic blood pressure that is reached with two or three antihypertensive agents (even if greater than 140 mmHg) may be a more reasonable interim goal [42]. (See 'J-shaped systolic curve' above and "Treatment of hypertension in the elderly patient, particularly isolated systolic hypertension", section on 'Importance of diastolic pressure' and "Treatment of hypertension in the elderly patient, particularly isolated systolic hypertension", section on 'Goal blood pressure'.)

- Lower goals are suggested for patients with certain comorbid conditions, such as those with atherosclerotic cardiovascular disease or in patients with proteinuric chronic kidney disease. In addition, antihypertensive drugs are given to improve survival in a number of conditions (eg, heart failure, post-myocardial infarction), independent of the blood pressure. In these cases, lower blood pressure levels may be accepted to permit sufficient drug doses. (See 'Lower goal in patients at increased risk' below and "Blood pressure management in patients with atherosclerotic cardiovascular disease", section on 'Goal blood pressure' and "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal'.)

- The goal blood pressure in diabetic patients without certain complications (ie, those who do not have proteinuric kidney disease or atherosclerotic cardiovascular disease) is controversial. Some professional societies and organizations recommend a blood pressure of <140/<90 mmHg, while others recommend more aggressive blood pressure lowering. These issues are discussed elsewhere. (See "Treatment of hypertension in patients with diabetes mellitus".)

The above recommendations and suggestions assume that the blood pressure is being accurately measured. They also assume that the blood pressure is being gradually reduced since acute lowering of the blood pressure in patients with severe underlying hypertension can lead to deleterious cerebrovascular and coronary events. (See "Blood pressure measurement in the diagnosis and management of hypertension in adults" and "Management of severe asymptomatic hypertension (hypertensive urgencies) in adults".)

Lower goal in patients at increased risk — A lower goal blood pressure than described in the preceding sections may be beneficial in the following clinical settings [42,43]; the supportive evidence and conflicting data are discussed elsewhere:

- Atherosclerotic cardiovascular disease. (See "Blood pressure management in patients with atherosclerotic cardiovascular disease", section on 'Goal blood pressure'.)

- Chronic kidney disease associated with proteinuria. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal'.)

- Heart failure. (See "Treatment of hypertension in patients with heart failure", section on 'Goal blood pressure'.)

Determining if patients are at goal — Whether blood pressure is measured in the clinic or at home, an average of multiple measurements provides a more accurate assessment of blood pressure control than single measurements. This issue is discussed in detail elsewhere. (See "Blood pressure measurement in the diagnosis and management of hypertension in adults", section on 'Need for multiple measurements'.)

Pulse pressure — The marked variations in risk of mortality with increased pulse pressure suggest that this parameter alone should **not** be used for prognostic or therapeutic decisions [4,44]. (See "Increased pulse pressure".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient information: High blood pressure in adults (Beyond the Basics)" and

"Patient information: High blood pressure treatment in adults (Beyond the Basics)" and "Patient information: High blood pressure, diet, and weight (Beyond the Basics)").

SUMMARY AND RECOMMENDATIONS

- Systolic and diastolic hypertension in the general population are defined as a blood pressure ≥140/≥90 mmHg measured on at least three separate occasions. Randomized controlled trials of antihypertensive therapy demonstrated significant cardiovascular benefit in patients with systolic and diastolic hypertension that was most pronounced in severe (diastolic pressures of 115 to 129 mmHg) and moderate (diastolic pressures of 105 to 114 mmHg) disease. The absolute benefit of blood pressure lowering is much lower in patients with mild hypertension (diastolic pressures of 90 to 104 mmHg) (figure 1). (See 'Systolic and diastolic hypertension' above.)

- There are no randomized trials that have evaluated the efficacy of treating mild hypertension in patients with baseline systolic pressures of 140 to 149 mmHg. The three largest randomized trials that have been performed in patients with mild hypertension were the Medical Research Council trial, the Hypertension Detection and Follow-up Program, and the FEVER trial. All showed significant benefit from antihypertensive therapy, which lowered the mean blood pressure to less than 140 mmHg systolic and/or less than 90 mmHg diastolic. (See 'Mild hypertension' above.)

- There is conflicting evidence related to the possible risk of excessive reduction in the diastolic blood pressure. Rather than demonstrating a progressive benefit at lower pressures, many trials revealed a J-shaped curve in which the risk of cardiac events declines as the diastolic pressure falls from above 100 mmHg to approximately 85 mmHg, but then rises back up at pressures below 80 to 85 mmHg (figure 4A-B and figure 5A and figure 5B). By comparison, there is little evidence suggesting a J-curve for the systolic blood pressure, other than perhaps isolated systolic hypertension (figure 4A-B and figure 5A and figure 5B). (See 'J-shaped diastolic curve' above.)

- Isolated systolic hypertension is considered to be present when the blood pressure is ≥140/<90 mmHg, and isolated diastolic hypertension, which is discussed elsewhere, is considered to be present when the blood pressure is <140/≥90 mmHg. Specific recommendations and supportive data are presented elsewhere. (See "Hypertension: Who should be treated?", section on 'Definitions' and "Hypertension: Who should be treated?", section on 'Isolated diastolic hypertension'.)

- The goal blood pressures presented below refer to the levels at which more intensive antihypertensive therapy to produce a further reduction in blood pressure is **not** recommended. These goals are broadly consistent with recommendations from major societies and organizations (see 'Goal blood pressure' above):

  - In the general hypertensive population of younger adults (ie, younger than 60 years of age), we recommend a goal blood pressure of <140/<90 mmHg.

  - In the general hypertensive population of older adults (ie, 60 years and older, nondiabetic, no chronic kidney disease), we recommend a goal blood pressure <150/<90 mmHg and, in patients aged 60 to 79 years, also suggest reducing systolic pressure to <140 mmHg if it can be achieved without producing significant side effects. In older patients with diabetes or chronic kidney disease, we recommend a blood pressure goal of <140/<90 mmHg, consistent with major societies and organizations.

    These systolic blood pressure targets also apply to older adults with isolated systolic hypertension. However, the diastolic blood pressure should be reduced to a minimum posttreatment diastolic pressure of >60 mmHg overall or perhaps >65 mmHg in patients with known coronary artery disease unless symptoms that could be attributable to hypoperfusion occur at higher pressures. In many cases, the level of systolic blood pressure that is reached with two or three antihypertensive agents (even if greater than 140 mmHg) may be a more reasonable interim goal. (See 'J-shaped systolic curve' above and "Treatment of hypertension in the elderly

patient, particularly isolated systolic hypertension", section on 'Importance of diastolic pressure' and "Treatment of hypertension in the elderly patient, particularly isolated systolic hypertension", section on 'Goal blood pressure'.)

- Lower goals are suggested for patients with certain comorbid conditions, such as those with atherosclerotic cardiovascular disease or in patients with proteinuric chronic kidney disease (defined as a urine protein excretion >500 to 1000 mg/day). In addition, antihypertensive drugs are given to improve survival in a number of conditions (eg, heart failure, post-myocardial infarction), independent of the blood pressure. In these cases, lower blood pressure levels may be accepted to permit sufficient drug doses. (See 'Lower goal in patients at increased risk' above and "Blood pressure management in patients with atherosclerotic cardiovascular disease", section on 'Goal blood pressure' and "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal'.)

- Whether blood pressure is measured in the clinic or at home, an average of multiple measurements provides a more accurate assessment of blood pressure control than single measurements. This issue is discussed in detail elsewhere. (See "Blood pressure measurement in the diagnosis and management of hypertension in adults", section on 'Need for multiple measurements'.)

REFERENCES

1. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995; 25:305.
2. Kannel WB. Elevated systolic blood pressure as a cardiovascular risk factor. Am J Cardiol 2000; 85:251.
3. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000; 355:865.
4. Pastor-Barriuso R, Banegas JR, Damián J, et al. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. Ann Intern Med 2003; 139:731.
5. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360:1903.
6. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31:1281.
7. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311:507.
8. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 1967; 202:1028.
9. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970; 213:1143.
10. Hebert PR, Moser M, Mayer J, et al. Recent evidence on drug therapy of mild to moderate hypertension and decreased risk of coronary heart disease. Arch Intern Med 1993; 153:578.
11. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. Br Med J (Clin Res Ed) 1985; 291:97.
12. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. JAMA 1979; 242:2562.

13. The effect of treatment on mortality in "mild" hypertension: results of the hypertension detection and follow-up program. N Engl J Med 1982; 307:976.
14. Liu L, Zhang Y, Liu G, et al. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens 2005; 23:2157.
15. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the american society of hypertension and the international society of hypertension. J Hypertens 2014; 32:3.
16. Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007; 115:2761.
17. Hackam DG, Quinn RR, Ravani P, et al. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2013; 29:528.
18. Wright Jr JT, Fine LJ, Lackland DT, et al. Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority View. Ann Intern Med 2014.
19. Kaplan NM. What is goal blood pressure for the treatment of hypertension? Arch Intern Med 2001; 161:1480.
20. Farnett L, Mulrow CD, Linn WD, et al. The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? JAMA 1991; 265:489.
21. D'Agostino RB, Belanger AJ, Kannel WB, Cruickshank JM. Relation of low diastolic blood pressure to coronary heart disease death in presence of myocardial infarction: the Framingham Study. BMJ 1991; 303:385.
22. Berl T, Hunsicker LG, Lewis JB, et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. J Am Soc Nephrol 2005; 16:2170.
23. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006; 144:884.
24. Dorresteijn JA, van der Graaf Y, Spiering W, et al. Relation between blood pressure and vascular events and mortality in patients with manifest vascular disease: J-curve revisited. Hypertension 2012; 59:14.
25. Sleight P, Redon J, Verdecchia P, et al. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. J Hypertens 2009; 27:1360.
26. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010; 304:61.
27. Boutitie F, Gueyffier F, Pocock S, et al. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. Ann Intern Med 2002; 136:438.
28. Staessen J, Bulpitt C, Clement D, et al. Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly. BMJ 1989; 298:1552.
29. Flack JM, Neaton J, Grimm R Jr, et al. Blood pressure and mortality among men with prior myocardial infarction. Multiple Risk Factor Intervention Trial Research Group. Circulation 1995; 92:2437.
30. Lazarus JM, Bourgoignie JJ, Buckalew VM, et al. Achievement and safety of a low blood pressure goal in chronic renal disease. The Modification of Diet in Renal Disease Study Group. Hypertension 1997; 29:641.
31. Bulpitt CJ, Palmer AJ, Fletcher AE, et al. Optimal blood pressure control in treated hypertensive patients. Report from the Department of Health Hypertension Care Computing Project (DHCCP). Circulation 1994; 90:225.
32. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991; 265:3255.
33. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril

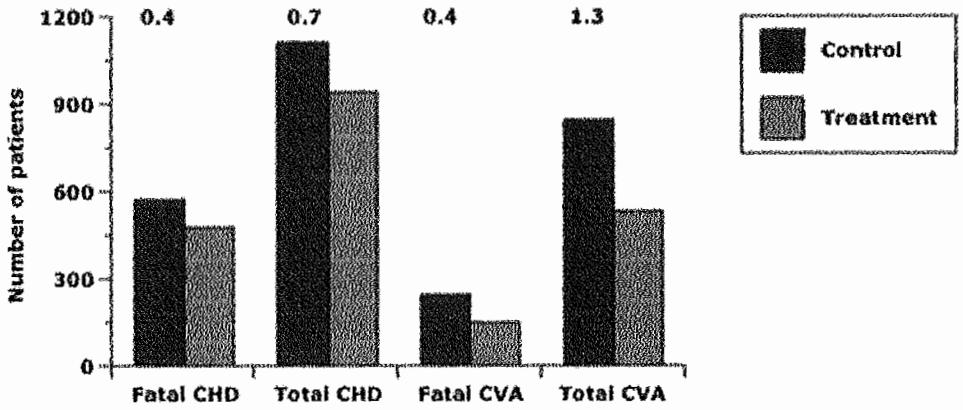
Study (INVEST): a randomized controlled trial. JAMA 2003; 290:2805.

34. Wang JG, Staessen JA, Franklin SS, et al. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. Hypertension 2005; 45:907.
35. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351:1755.
36. Kaplan N. J-curve not burned off by HOT study. Hypertension Optimal Treatment. Lancet 1998; 351:1748.
37. Zanchetti A, Hansson L, Clement D, et al. Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? J Hypertens 2003; 21:797.
38. Lund-Johansen P. Intensive blood pressure treatment: beneficial for all but the smoking hypertensives? J Hypertens 2003; 21:697.
39. Vokó Z, Bots ML, Hofman A, et al. J-shaped relation between blood pressure and stroke in treated hypertensives. Hypertension 1999; 34:1181.
40. Somes GW, Pahor M, Shorr RI, et al. The role of diastolic blood pressure when treating isolated systolic hypertension. Arch Intern Med 1999; 159:2004.
41. Shorr RI, Somes GW. Can Diastolic Blood Pressure be Excessively Lowered in the Treatment of Isolated Systolic Hypertension? J Clin Hypertens (Greenwich) 2000; 2:134.
42. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289:2560.
43. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004; 43:S1.
44. Blacher J, Staessen JA, Girerd X, et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. Arch Intern Med 2000; 160:1085.

Topic 3861 Version 13.0

GRAPHICS

Cardiovascular benefit of treating mild hypertension

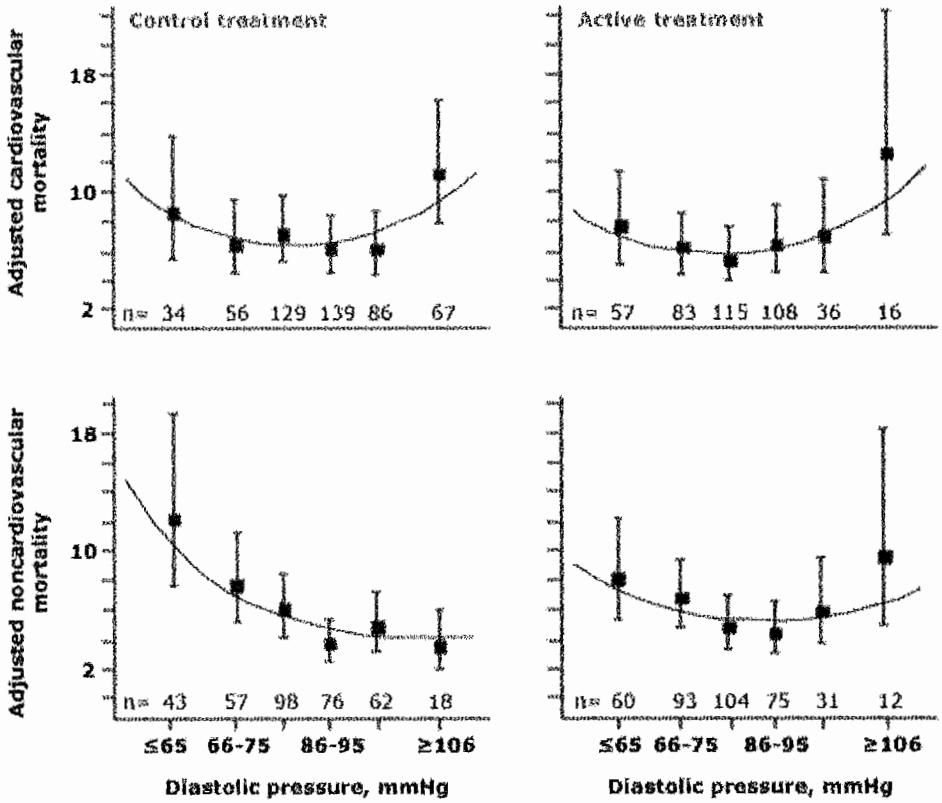


Reduced incidence of fatal and total coronary heart disease (CHD) events and strokes following antihypertensive therapy in 17 controlled studies involving almost 48,000 patients with mild to moderate hypertension. The number of patients having each of these events is depicted, with active treatment lowering the incidence of coronary events by 16 percent and stroke by 40 percent. However, the absolute benefit - as shown, in percent, by the numbers at the top of the graph - was much less. Treatment for approximately 4 to 5 years prevented a coronary event or a stroke in two percent of patients (0.7 + 1.3), including prevention of death in 0.8 percent. CVA = cerebrovascular accident (stroke).

Data from: Hebert PR, Moser M, Mayer J, et al. Arch Intern Med 1993; 153:578.

Graphic 52231 Version 2.0

Lack of true J-shaped curve in diastolic pressure

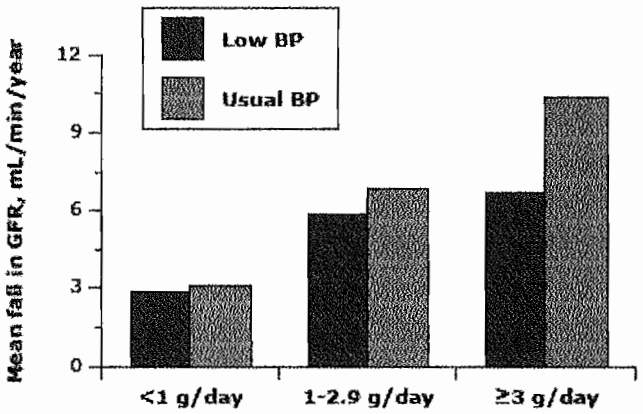


Age- and sex-adjusted mortality rates (per 1000 patient years, bars show the 95 percent confidence intervals) according to achieved diastolic pressure in active treatment and control groups in a meta-analysis of seven randomized clinical trials of hypertensive patients. The number of events is shown below each bar. Among treated patients, cardiovascular mortality initially falls at achieved diastolic pressures below 106 mmHg and then rises again at low diastolic pressures (upper right panel). However, a similar relationship is seen with noncardiovascular mortality (bottom right panel) and in the control groups (left panels). Thus, the increase in mortality at low systolic pressures probably reflects underlying poor health rather than an adverse effect of antihypertensive therapy.

Data from Boutitie, F, Gueyffier, F, Pocock, S, et al, Ann Intern Med 2002; 136:438.

Graphic 73430 Version 2.0

Aggressive BP control preserves renal function in proteinuric patients

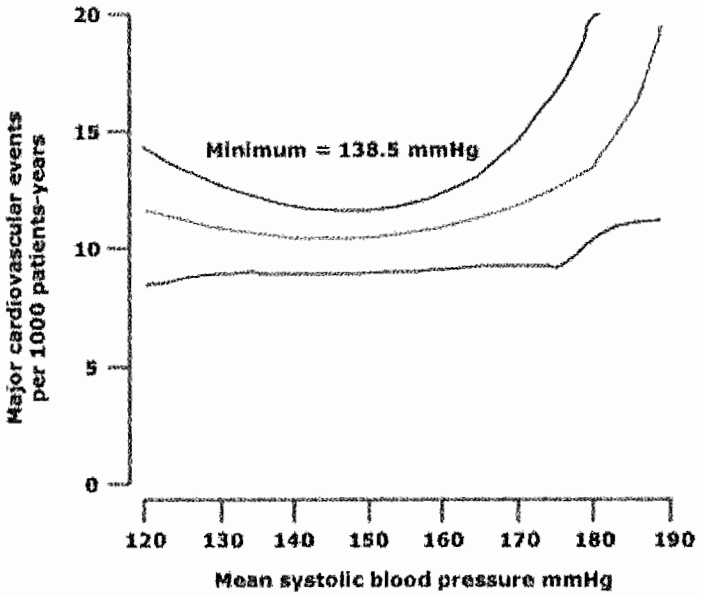


Mean fall in glomerular filtration rate (GFR) according to the degree of proteiuria in patients treated with usual blood pressure control (mean BP about 130/80) or with more aggressive antihypertensive therapy in which the mean BP was 4.7 mmHg lower over a three year period. The rate of fall in GFR varied directly with protein excretion and the benefit of aggressive BP control was absent in the 420 patients excreting less than 1 g/day, modest in the 104 patients excreting between 1 and 3 g/day, and substantial (3.5 mL/min per year slower) and statistically significant in the 54 patients excreting at least 3 g/day.

Data from: Klahr S, Levey AS, Beck GJ, et al. N Engl J Med 1994; 330:877.

Graphic 78190 Version 3.0

Systolic pressure and cardiovascular events in HOT trial

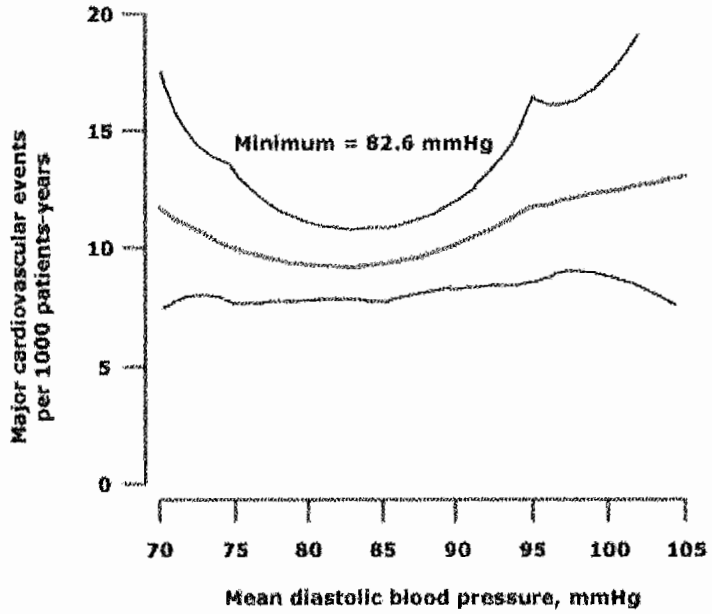


Estimated incidence (95 percent CI) of major cardiovascular events in relation to achieved mean systolic blood pressure in the HOT trial. The systolic pressure at the lowest point of the curve is indicated (minimum).

Adapted from Hansson, L, Zanchetti, A, Carruthers, SG, et al, Lancet 1998; 351:1755.

Graphic 55532 Version 2.0

Diastolic pressure and cardiovascular events in HOT trial

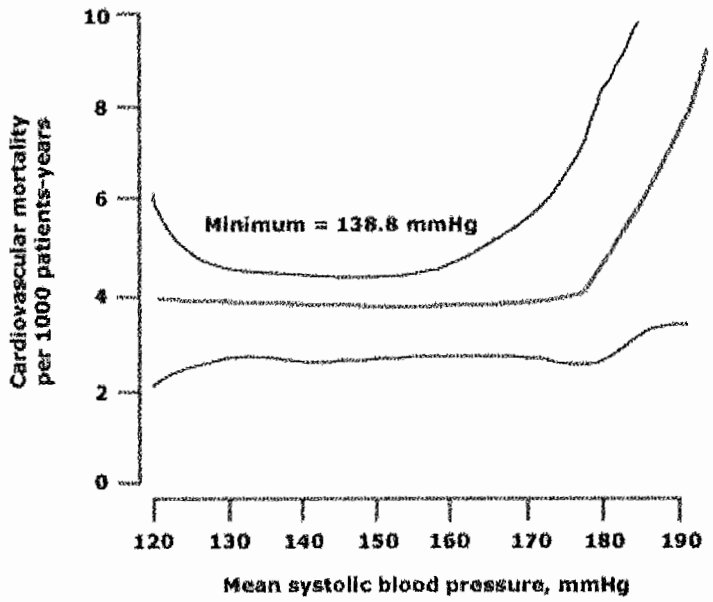


Estimated incidence (95 percent CI) of major cardiovascular events in relation to achieved mean diastolic blood pressure in the HOT trial. The diastolic pressure at the lowest point of the curve is indicated (minimum).

Adapted from Hansson, L, Zanchetti, A, Carruthers, SG, et al, Lancet 1998; 351:1755.

Graphic 81362 Version 2.0

Systolic pressure and cardiovascular mortality in HOT trial

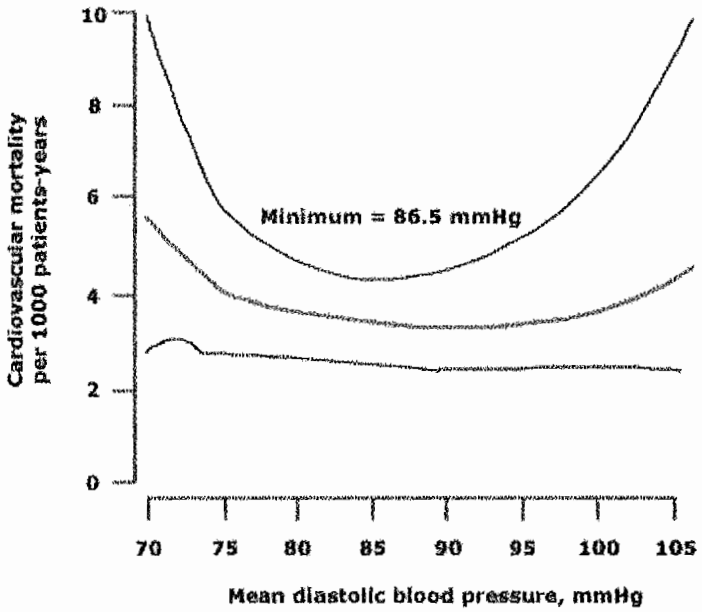


Estimated incidence (95 percent CI) of cardiovascular mortality in relation to achieved mean systolic blood pressure in the HOT trial. The systolic pressure at the lowest point of the curve is indicated (minimum).

Adapted from: Hansson L, Zanchetti A, Carruthers SG, et al. Lancet 1998; 351:1755.

Graphic 75482 Version 2.0

Diastolic pressure and cardiovascular mortality in HOT trial

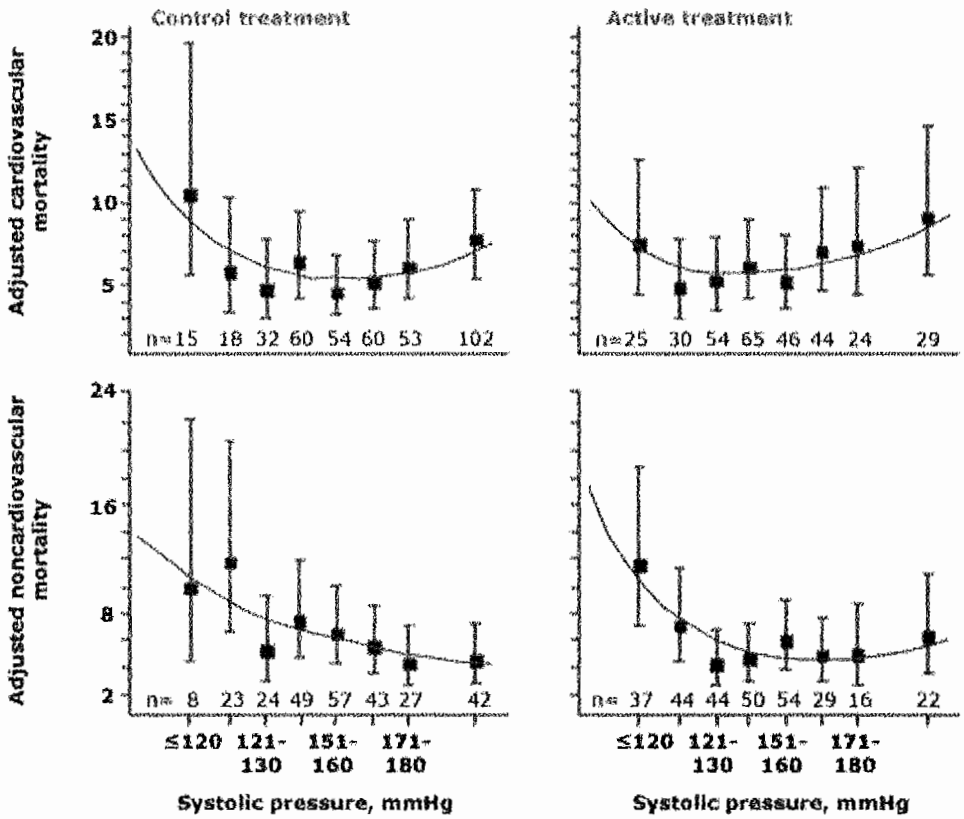


Estimated incidence (95 percent CI) of cardiovascular mortality in relation to achieved mean diastolic blood pressure in the HOT trial. The diastolic pressure at the lowest point of the curve is indicated (minimum).

Adapted from: Hansson L, Zanchetti A, Carruthers SG, et al. Lancet 1998; 351:1755.

Graphic 71321 Version 2.0

Lack of true J-shaped curve in systolic pressure



Age- and sex-adjusted mortality rates (per 1000 patient years, bars show the 95 percent confidence intervals) according to achieved systolic pressure in active treatment and control groups in a meta-analysis of seven randomized clinical trials of hypertensive patients. The number of events is shown below each bar. Among treated patients, cardiovascular mortality initially falls at achieved systolic pressures below 180 mmHg and then rises again at low systolic pressures (upper right panel). However, a similar relationship is seen with noncardiovascular mortality (bottom right panel) and in the control groups (left panels). Thus, the increase in mortality at low diastolic pressures probably reflects underlying poor health rather than an adverse effect of antihypertensive therapy.

Data from Boutitie, F, Gueyffier, F, Pocock, S, et al, Ann Intern Med 2002; 136:438.

Graphic 80901 Version 1.0

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden, while clinicians want guidance on hypertension management using the best scientific evidence. This report takes a rigorous, evidence-based approach to recommend treatment thresholds, goals, and medications in the management of hypertension in adults. Evidence was drawn from randomized controlled trials, which represent the gold standard for determining efficacy and effectiveness. Evidence quality and recommendations were graded based on their effect on important outcomes.

There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy. There is moderate evidence to support initial or add-on antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in persons with CKD to improve kidney outcomes.

Although this guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.

Editorial pages 472, 474, and 477

Author Audio Interview at jama.com

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 522

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Paul A. James, MD, University of Iowa, 200 Hawkins Dr, 01286-D PFP, Iowa City, IA 52242-1097 (paul-james@uiowa.edu).

JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427
Published online December 18, 2013.

Hypertension remains one of the most important preventable contributors to disease and death. Abundant evidence from randomized controlled trials (RCTs) has shown benefit of antihypertensive drug treatment in reducing important health outcomes in persons with hypertension.[1-3] Clinical guidelines are at the intersection between research evidence and clinical actions that can improve patient outcomes. The Institute of Medicine Report *Clinical Practice Guidelines We Can Trust* outlined a pathway to guideline development and is the approach that this panel aspired to in the creation of this report.[4]

The panel members appointed to the Eighth Joint National Committee (JNC 8) used rigorous evidence-based methods, developing Evidence Statements and recommendations for blood pressure (BP) treatment based on a systematic review of the literature to meet user needs, especially the needs of the primary care clinician. This report is an executive summary of the evidence and is designed to provide clear recommendations for all clinicians. Major differences from the previous JNC report are summarized in Table 1. The complete evidence summary and detailed description of the evidence review and methods are provided online (see Supplement).

ACEI *angiotensin-converting enzyme inhibitor*
ARB *angiotensin receptor blocker*
BP *blood pressure*
CCB *calcium channel blocker*
CKD *chronic kidney disease*
CVD *cardiovascular disease*
ESRD *end-stage renal disease*
GFR *glomerular filtration rate*
HF *heart failure*

The Process

The panel members appointed to JNC 8 were selected from more than 400 nominees based on expertise in hypertension (n = 14), primary care (n = 6), including geriatrics (n = 2), cardiology (n = 2), nephrology (n = 3), nursing (n = 1), pharmacology (n = 2), clinical trials (n = 6), evidence-based medicine (n = 3), epidemiology (n = 1), informatics (n = 4), and the development and implementation of clinical guidelines in systems of care (n = 4).

The panel also included a senior scientist from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a senior medical officer from the National Heart, Lung, and Blood Institute (NHLBI), and a senior scientist from NHLBI, who withdrew from authorship prior to publication. Two members left the panel early in the process before the evidence review because of new job commitments that prevented them from continuing to serve. Panel members disclosed any potential conflicts of interest including studies evaluated in this report and relationships with industry. Those with conflicts were allowed to participate in discussions as long as they declared their relationships, but they recused themselves from voting on evidence statements and recommendations relevant to their relationships or conflicts. Four panel members (24%) had relationships with industry or potential conflicts to disclose at the outset of the process.

In January 2013, the guideline was submitted for external peer review by NHLBI to 20 reviewers, all of whom had expertise in hypertension, and to 16 federal agencies. Reviewers also had expertise in cardiology, nephrology, primary care, pharmacology, research (including clinical trials), biostatistics, and other important related fields. Sixteen individual reviewers and 5 federal agencies responded. Reviewers' comments were collected, collated, and anonymized. Comments were reviewed and discussed by the panel from March through June 2013 and incorporated into a revised document. (Reviewers' comments and suggestions, and responses and disposition by the panel are available on request from the authors.)

Questions Guiding the Evidence Review

This evidence-based hypertension guideline focuses on the panel's 3 highest-ranked questions related to high BP management identified through a modified Delphi technique.[5] Nine recommendations are made reflecting these questions. These questions address thresholds and goals for pharmacologic treatment of hypertension and whether particular antihypertensive drugs or drug classes improve important health outcomes compared with other drug classes.

1. In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
2. In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

The Evidence Review

The evidence review focused on adults aged 18 years or older with hypertension and included studies with the following prespecified subgroups: diabetes, coronary artery disease, peripheral artery disease, heart failure, previous stroke, chronic kidney disease (CKD), proteinuria, older adults, men and women, racial and ethnic groups, and smokers. Studies with sample sizes smaller than 100 were excluded, as were studies with a follow-up period of less than 1 year, because small studies of brief duration are unlikely to yield enough health-related outcome information to permit interpretation of treatment effects. Studies were included in the evidence review only if they reported the effects of the studied interventions on any of these important health outcomes:

- Overall mortality, cardiovascular disease (CVD)–related mortality, CKD-related mortality
- Myocardial infarction, heart failure, hospitalization for heart failure, stroke
- Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), other revascularization (includes carotid, renal, and lower extremity revascularization)
- End-stage renal disease (ESRD) (ie, kidney failure resulting in dialysis or transplantation), doubling of creatinine level, halving of glomerular filtration rate (GFR).

The panel limited its evidence review to RCTs because they are less subject to bias than other study designs and represent the gold standard for determining efficacy and effectiveness.[6] The studies

Table 1. Comparison of Current Recommendations With JNC 7 Guidelines

Topic	JNC 7	2014 Hypertension Guideline
Methodology	Nonsystematic literature review by expert committee including a range of study designs Recommendations based on consensus	Critical questions and review criteria defined by expert panel with input from methodology team Initial systematic review by methodologists restricted to RCT evidence Subsequent review of RCT evidence and recommendations by the panel according to a standardized protocol
Definitions	Defined hypertension and prehypertension	Definitions of hypertension and prehypertension not addressed, but thresholds for pharmacologic treatment were defined
Treatment goals	Separate treatment goals defined for "uncomplicated" hypertension and for subsets with various comorbid conditions (diabetes and CKD)	Similar treatment goals defined for all hypertensive populations except when evidence review supports different goals for a particular subpopulation
Lifestyle recommendations	Recommended lifestyle modifications based on literature review and expert opinion	Lifestyle modifications recommended by endorsing the evidence-based Recommendations of the Lifestyle Work Group
Drug therapy	Recommended 5 classes to be considered as initial therapy but recommended thiazide-type diuretics as initial therapy for most patients without compelling indication for another class Specified particular antihypertensive medication classes for patients with compelling indications, ie, diabetes, CKD, heart failure, myocardial infarction, stroke, and high CVD risk Included a comprehensive table of oral antihypertensive drugs including names and usual dose ranges	Recommended selection among 4 specific medication classes (ACEI or ARB, CCB or diuretics) and doses based on RCT evidence Recommended specific medication classes based on evidence review for racial, CKD, and diabetic subgroups Panel created a table of drugs and doses used in the outcome trials
Scope of topics	Addressed multiple issues (blood pressure measurement methods, patient evaluation components, secondary hypertension, adherence to regimens, resistant hypertension, and hypertension in special populations) based on literature review and expert opinion	Evidence review of RCTs addressed a limited number of questions, those judged by the panel to be of highest priority.
Review process prior to publication	Reviewed by the National High Blood Pressure Education Program Coordinating Committee, a coalition of 39 major professional, public, and voluntary organizations and 7 federal agencies	Reviewed by experts including those affiliated with professional and public organizations and federal agencies; no official sponsorship by any organization should be inferred

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; JNC, Joint National Committee; RCT, randomized controlled trial

in the evidence review were from original publications of eligible RCTs. These studies were used to create evidence tables and summary tables that were used by the panel for their deliberations (see Supplement). Because the panel conducted its own systematic review using original studies, systematic reviews and meta-analyses of RCTs conducted and published by other groups were not included in the formal evidence review.

Initial search dates for the literature review were January 1, 1966, through December 31, 2009. The search strategy and PRISMA diagram for each question is in the online Supplement. To ensure that no major relevant studies published after December 31, 2009, were excluded from consideration, 2 independent searches of PubMed and CINAHL between December 2009 and August 2013 were conducted with the same MeSH terms as the original search. Three panel members reviewed the results. The panel limited the inclusion criteria of this second search to the following. (1) The study was a major study in hypertension (eg, ACCORD-BP, SPS3; however, SPS3 did not meet strict inclusion criteria because it included nonhypertensive participants. SPS3 would not have changed our conclusions/recommendations because the only significant finding supporting a lower goal for BP occurred in an infrequent secondary outcome).[7,8] (2) The study had at least 2000 participants. (3) The study was multicentered. (4) The study met all the other inclusion/exclusion criteria. The relatively high threshold of 2000 participants was used because of the markedly lower event rates observed in recent RCTs such as ACCORD, suggesting that larger study populations are needed to obtain interpretable results. Additionally, all panel members were asked to identify newly published studies for consideration if they met the above criteria. No additional clinical trials met the previously described inclusion criteria. Studies selected were rated for quality using NHLBI's standardized quality rating tool (see Supplement) and were only included if rated as good or fair.

An external methodology team performed the literature review, summarized data from selected papers into evidence tables, and provided a summary of the evidence. From this evidence review, the panel crafted evidence statements and voted on agreement or disagreement with each statement. For approved evidence statements, the panel then voted on the quality of the evidence (**Table 2**). Once all evidence statements for each critical question were identified, the panel reviewed the evidence statements to craft the clinical recommendations, voting on each recommendation and on the strength of the recommendation (**Table 3**). For both evidence statements and recommendations, a record of the vote count (for, against, or recusal) was made without attribution. The panel attempted to achieve 100% consensus whenever possible, but a two-thirds majority was considered acceptable, with the exception of recommendations based on expert opinion, which required a 75% majority agreement to approve.

Results (Recommendations)

The following recommendations are based on the systematic evidence review described above (**Box**). Recommendations 1 through 5 address questions 1 and 2 concerning thresholds and goals for BP treatment. Recommendations 6, 7, and 8 address question 3 concerning selection of antihypertensive drugs. Recommendation 9 is a summary of strategies based on expert opinion for starting and adding antihypertensive drugs. The evidence statements supporting the recommendations are in the online Supplement.

Table 2. Evidence Quality Rating

Type of Evidence	Quality Rating[a]
Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes Well-conducted meta-analyses of such studies Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect	High
RCTs with minor limitations affecting confidence in, or applicability of, the results Well-designed, well-executed non-randomized controlled studies and well-designed, well-executed observational studies Well-conducted meta-analyses of such studies Moderately certain about the estimate of effect; further research may have an impact on our confidence in the estimate of effect and may change the estimate	Moderate
RCTs with major limitations Non-randomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports) Physiological studies in humans Meta-analyses of such studies Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.	Low

Abbreviations: RCT, randomized controlled trial

[a]The evidence quality rating system used in this guideline was developed by the National Heart, Lung, and Blood Institute's (NHLBI's) Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI CVD guideline panels and work groups during this project. As a result, it includes the evidence quality rating for many types of studies, including studies that were not used in this guideline. Additional details regarding the evidence quality rating system are available in the online Supplement.

Table 3. Strength of Recommendation

Grade	Strength of Recommendation
A	Strong Recommendation There is high certainty based on evidence that the net benefit[a] is substantial.
B	Moderate Recommendation There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.
C	Weak Recommendation There is at least moderate certainty based on evidence that there is a small net benefit.
D	Recommendation against There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.
E	Expert Opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
N	No Recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the committee thought no recommendation should be made. Further research is recommended in this area.

The strength of recommendation grading system used in this guideline was developed by the National Heart, Lung, and Blood Institute's (NHLBI's) Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI CVD guideline panels and work groups during this project. Additional details regarding the strength of recommendation grading system are available in the online Supplement.

[a]Net benefit is defined as benefits minus the risks/harms of the service/intervention.

Recommendation 1

In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher and treat to a goal SBP lower than 150 mm Hg and goal DBP lower than 90 mm Hg.

Strong Recommendation – Grade A

Corollary Recommendation

In the general population aged 60 years or older, if pharmacologic treatment for high BP results in lower achieved SBP (for example, <140 mm Hg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.

Expert Opinion – Grade E

Recommendation 1 is based on evidence statements 1 through 3 from question 2 in which there is moderate- to high-quality evidence from RCTs that in the general population aged 60 years or older, treating high BP to a goal of lower than 150/90 mm Hg reduces stroke, heart failure, and coronary heart disease (CHD). There is also evidence (albeit low quality) from evidence statement 6, question 2 that setting a goal SBP of lower than 140 mm Hg in this age group provides no additional benefit compared with a higher goal SBP of 140 to 160 mm Hg or 140 to 149 mm Hg.[9,10]

To answer question 2 about goal BP, the panel reviewed all RCTs that met the eligibility criteria and that either compared treatment with a particular goal vs no treatment or placebo or compared treatment with one BP goal with treatment to another BP goal. The trials on which these evidence statements and this recommendation are based include HYVET, Syst-Eur, SHEP, JATOS, VALISH, and CARDIO-SIS.[1-3,9-11] Strengths, limitations, and other considerations related to this evidence review are presented in the evidence statement narratives and clearly support the benefit of treating to a BP lower than 150 mm Hg.

The corollary to recommendation 1 reflects that there are many treated hypertensive patients aged 60 years or older in whom SBP is currently lower than 140 mm Hg, based on implementation of previous guideline recommendations.[12] The panel's opinion is that in these patients, it is not necessary to adjust medication to allow BP

Box. Recommendations for Management of Hypertension

Recommendation 1
In the general population aged ≥60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥150 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg. (Strong Recommendation – Grade A)

Corollary Recommendation
In the general population aged ≥60 years, if pharmacologic treatment for high BP results in lower achieved SBP (eg, <140 mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)

Recommendation 2
In the general population <60 years, initiate pharmacologic treatment to lower BP at DBP ≥90 mm Hg and treat to a goal DBP <90 mm Hg. (For ages 30-59 years, Strong Recommendation – Grade A; For ages 18-29 years, Expert Opinion – Grade E)

Recommendation 3
In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg and treat to a goal SBP <140 mm Hg. (Expert Opinion – Grade E)

Recommendation 4
In the population aged ≥18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)

Recommendation 5
In the population aged ≥18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)

Recommendation 6
In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)

Recommendation 7
In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general black population: Moderate Recommendation – Grade B; for black patients with diabetes: Weak Recommendation – Grade C)

Recommendation 8
In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation – Grade B)

Recommendation 9
The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed. (Expert Opinion – Grade E)

to increase. In 2 of the trials that provide evidence supporting an SBP goal lower than 150 mm Hg, the average treated SBP was 143 to 144 mm Hg.[2,3] Many participants in those studies achieved an SBP lower than 140 mm Hg with treatment that was generally well tolerated. Two other trials[9,10] suggest there was no benefit for an SBP goal lower than 140 mm Hg, but the confidence intervals around the effect sizes were wide and did not exclude the possibility of a clinically important benefit. Therefore, the panel included a corollary recommendation based on expert opinion that treatment for hypertension does not need to be adjusted if treatment results in SBP lower than 140 mm Hg and is not associated with adverse effects on health or quality of life.

While all panel members agreed that the evidence supporting recommendation 1 is very strong, the panel was unable to reach unanimity on the recommendation of a goal SBP of lower than 150 mm Hg. Some members recommended continuing the JNC 7 SBP goal of lower than 140 mm Hg for individuals older than 60 years based on expert opinion.[12] These members concluded that the evidence was insufficient to raise the SBP target from lower than 140 to lower than 150 mm Hg in high-risk groups, such as black persons, those with CVD including stroke, and those with multiple risk factors. The panel agreed that more research is needed to identify optimal goals of SBP for patients with high BP.

Recommendation 2

In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at DBP of 90 mm Hg or higher and treat to a goal DBP of lower than 90 mm Hg.
For ages 30 through 59 years, Strong Recommendation – Grade A
For ages 18 through 29 years, Expert Opinion – Grade E

Recommendation 2 is based on high-quality evidence from 5 DBP trials (HDFP, Hypertension-Stroke Cooperative, MRC, ANBP, and VA Cooperative) that demonstrate improvements in health outcomes among adults aged 30 through 69 years with elevated BP.[13-18] Initiation of antihypertensive treatment at a DBP threshold of 90 mm Hg or higher and treatment to a DBP goal of lower than 90 mm Hg reduces cerebrovascular events, heart failure, and overall mortality (question 1, evidence statements 10, 11, 13; question 2, evidence statement 10). In further support for a DBP goal of lower than 90 mm Hg, the panel found evidence that there is no benefit in treating patients to a goal of either 80 mm Hg or lower or 85 mm Hg or lower compared with 90 mm Hg or lower based on the HOT trial, in which patients were randomized to these 3 goals without statistically significant differences between treatment groups in the primary or secondary outcomes (question 2, evidence statement 14).[19]

In adults younger than 30 years, there are no good- or fair-quality RCTs that assessed the benefits of treating elevated DBP on health outcomes (question 1, evidence statement 14). In the absence of such evidence, it is the panel's opinion that in adults younger than 30 years, the DBP threshold and goal should be the same as in adults 30 through 59 years of age.

Recommendation 3

In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher and treat to a goal SBP of lower than 140 mm Hg.
Expert Opinion – Grade E

Recommendation 3 is based on expert opinion. While there is high-quality evidence to support a specific SBP threshold and goal for persons aged 60 years or older (See recommendation 1), the panel found insufficient evidence from good- or fair-quality RCTs to support a specific SBP threshold or goal for persons younger than 60 years. In the absence of such evidence, the panel recommends an SBP treatment threshold of 140 mm Hg or higher and an SBP treatment goal of lower than 140 mm Hg based on several factors.

First, in the absence of any RCTs that compared the current SBP standard of 140 mm Hg with another higher or lower standard in this age group, there was no compelling reason to change current recommendations. Second, in the DBP trials that demonstrated the benefit of treating DBP to lower than 90 mm Hg, many of the study participants who achieved DBP of lower than 90 mm Hg were also likely to have achieved SBPs of lower than 140 mm Hg with treatment. It is not possible to determine whether the outcome benefits in these trials were due to lowering DBP, SBP, or both. Third, given the recommended SBP goal of lower than 140 mm Hg in adults with diabetes or CKD (recommendations 4 and 5), a similar SBP goal for the general population younger than 60 years may facilitate guideline implementation.

Recommendation 4

In the population aged 18 years or older with CKD, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher and treat to goal SBP of lower than 140 mm Hg and goal DBP lower than 90 mm Hg.

Expert Opinion – Grade E

Based on the inclusion criteria used in the RCTs reviewed by the panel, this recommendation applies to individuals younger than 70 years with an estimated GFR or measured GFR less than 60 mL/min/1.73 m^2 and in people of any age with albuminuria defined as greater than 30 mg of albumin/g of creatinine at any level of GFR.

Recommendation 4 is based on evidence statements 15-17 from question 2. In adults younger than 70 years with CKD, the evidence is insufficient to determine if there is a benefit in mortality, or cardiovascular or cerebrovascular health outcomes with antihypertensive drug therapy to a lower BP goal (for example, <130/80 mm Hg) compared with a goal of lower than 140/90 mm Hg (question 2, evidence statement 15). There is evidence of moderate quality demonstrating no benefit in slowing the progression of kidney disease from treatment with antihypertensive drug therapy to a lower BP goal (for example, <130/80 mm Hg) compared with a goal of lower than 140/90 mm Hg (question 2, evidence statement 16).

Three trials that met our criteria for review addressed the effect of antihypertensive drug therapy on change in GFR or time to development of ESRD, but only one trial addressed cardiovascular disease end points. Blood pressure goals differed across the trials, with 2 trials (AASK and MDRD) using mean arterial pressure and different targets by age, and 1 trial (REIN-2) using only DBP goals.[20-22] None of the trials showed that treatment to a lower BP goal (for example, <130/80 mm Hg) significantly lowered kidney or cardiovascular disease end points compared with a goal of lower than 140/90 mm Hg.

For patients with proteinuria (>3 g/24 hours), post hoc analysis from only 1 study (MDRD) indicated benefit from treatment to a lower BP goal (<130/80 mm Hg), and this related to kidney outcomes only.[22] Although post hoc observational analyses of data from this trial and others suggested benefit from the lower goal at lower levels of proteinuria, this result was not seen in the primary analyses or in AASK or REIN-2 (question 2, evidence statement 17).[20,21]

Based on available evidence the panel cannot make a recommendation for a BP goal for people aged 70 years or older with GFR less than 60 mL/min/1.73m^2. The commonly used estimating equations for GFR were not developed in populations with significant numbers of people older than 70 years and have not been validated in older adults. No outcome trials reviewed by the panel included large numbers of adults older than 70 years with CKD. Further, the diagnostic criteria for CKD do not consider age-related decline in kidney function as reflected in estimated GFR. Thus, when weighing the risks and benefits of a lower BP goal for people aged 70 years or older with estimated GFR less than 60 mL/min/1.73m^2, antihypertensive treatment should be individualized, taking into consideration factors such as frailty, comorbidities, and albuminuria.

Recommendation 5

In the population aged 18 years or older with diabetes, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher and treat to a goal SBP of lower than 140 mm Hg and goal DBP lower than 90 mm Hg.

Expert Opinion – Grade E

Recommendation 5 is based on evidence statements 18-21 from question 2, which address BP goals in adults with both diabetes and hypertension. There is moderate-quality evidence from 3 trials (SHEP, Syst-Eur, and UKPDS) that treatment to an SBP goal of lower than 150 mm Hg improves cardiovascular and cerebrovascular health outcomes and lowers mortality (see question 2, evidence statement 18) in adults with diabetes and hypertension.[23-25] No RCTs addressed whether treatment to an SBP goal of lower than 140 mm Hg compared with a higher goal (for example, <150 mm Hg) improves health outcomes in adults with diabetes and hypertension. In the absence of such evidence, the panel recommends an SBP goal of lower than 140 mm Hg and a DBP goal lower than 90 mm Hg in this population based on expert opinion, consistent with the BP goals in recommendation 3 for the general population younger than 60 years with hypertension. Use of a consistent BP goal in the general population younger than 60 years and in adults with diabetes of any age may facilitate guideline implementation. This recommendation for an SBP goal of lower than 140 mm Hg in patients with diabetes is also supported by the ACCORD-BP trial, in which the control group used this goal and had similar outcomes compared with a lower goal.[7]

The panel recognizes that the ADVANCE trial tested the effects of treatment to lower BP on major macrovascular and microvascular events in adults with diabetes who were at increased risk of CVD, but the study did not meet the panel's inclusion criteria because participants were eligible irrespective of baseline BP, and there were no randomized BP treatment thresholds or goals.[26]

The panel also recognizes that an SBP goal of lower than 130 mm Hg is commonly recommended for adults with diabetes and hypertension. However, this lower SBP goal is not supported by any RCT that randomized participants into 2 or more groups in which

treatment was initiated at a lower SBP threshold than 140 mm Hg or into treatment groups in which the SBP goal was lower than 140 mm Hg and that assessed the effects of a lower SBP threshold or goal on important health outcomes. The only RCT that compared an SBP treatment goal of lower than 140 mm Hg with a lower SBP goal and assessed the effects on important health outcomes is ACCORD-BP, which compared an SBP treatment goal of lower than 120 mm Hg with a goal lower than 140 mm Hg.[7] There was no difference in the primary outcome, a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. There were also no differences in any of the secondary outcomes except for a reduction in stroke. However, the incidence of stroke in the group treated to lower than 140 mm Hg was much lower than expected, so the absolute difference in fatal and nonfatal stroke between the 2 groups was only 0.21% per year. The panel concluded that the results from ACCORD-BP did not provide sufficient evidence to recommend an SBP goal of lower than 120 mm Hg in adults with diabetes and hypertension.

The panel similarly recommends the same goal DBP in adults with diabetes and hypertension as in the general population (<90 mm Hg). Despite some existing recommendations that adults with diabetes and hypertension should be treated to a DBP goal of lower than 80 mm Hg, the panel did not find sufficient evidence to support such a recommendation. For example, there are no good- or fair-quality RCTs with mortality as a primary or secondary prespecified outcome that compared a DBP goal of lower than 90 mm Hg with a lower goal (evidence statement 21).

In the HOT trial, which is frequently cited to support a lower DBP goal, investigators compared a DBP goal of 90 mm Hg or lower vs a goal of 80 mm Hg or lower.[19] The lower goal was associated with a reduction in a composite CVD outcome (question 2, evidence statement 20), but this was a post hoc analysis of a small subgroup (8%) of the study population that was not prespecified. As a result, the evidence was graded as low quality.

Another commonly cited study to support a lower DBP goal is UKPDS,[25] which had a BP goal of lower than 150/85 mm Hg in the more-intensively treated group compared with a goal of lower than 180/105 mm Hg in the less-intensively treated group. UKPDS did show that treatment in the lower goal BP group was associated with a significantly lower rate of stroke, heart failure, diabetes-related end points, and deaths related to diabetes. However, the comparison in UKPDS was a DBP goal of lower than 85 mm Hg vs lower than105 mm Hg; therefore, it is not possible to determine whether treatment to a DBP goal of lower than 85 mm Hg improves outcomes compared with treatment to a DBP goal of lower than 90 mm Hg. In addition, UKPDS was a mixed systolic and diastolic BP goal study (combined SBP and DBP goals), so it cannot be determined if the benefits were due to lowering SBP, DBP, or both.

Recommendation 6

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).
Moderate Recommendation – Grade B

For this recommendation, only RCTs that compared one class of antihypertensive medication to another and assessed the effects on health outcomes were reviewed; placebo-controlled RCTs were not included. However, the evidence review was informed by major placebo-controlled hypertension trials, including 3 federally funded trials (VA Cooperative Trial, HDFP, and SHEP), that were pivotal in demonstrating that treatment of hypertension with antihypertensive medications reduces cardiovascular or cerebrovascular events and/or mortality.[3,13,18] These trials all used thiazide-type diuretics compared with placebo or usual care as the basis of therapy. Additional evidence that BP lowering reduces risk comes from trials of β-blocker vs placebo[16,27] and CCB vs placebo.[1]

Each of the 4 drug classes recommended by the panel in recommendation 6 yielded comparable effects on overall mortality and cardiovascular, cerebrovascular, and kidney outcomes, with one exception: heart failure. Initial treatment with a thiazide-type diuretic was more effective than a CCB or ACEI (question 3, evidence statements 14 and 15), and an ACEI was more effective than a CCB (question 3, evidence statement 1) in improving heart failure outcomes. While the panel recognized that improved heart failure outcomes was an important finding that should be considered when selecting a drug for initial therapy for hypertension, the panel did not conclude that it was compelling enough within the context of the overall body of evidence to preclude the use of the other drug classes for initial therapy. The panel also acknowledged that the evidence supported BP control, rather than a specific agent used to achieve that control, as the most relevant consideration for this recommendation.

The panel did not recommend β-blockers for the initial treatment of hypertension because in one study use of β-blockers resulted in a higher rate of the primary composite outcome of cardiovascular death, myocardial infarction, or stroke compared to use of an ARB, a finding that was driven largely by an increase in stroke (question 3, evidence statement 22).[28] In the other studies that compared a β-blocker to the 4 recommended drug classes, the β-blocker performed similarly to the other drugs (question 3, evidence statement 8) or the evidence was insufficient to make a determination (question 3, evidence statements 7, 12, 21, 23, and 24).

α-Blockers were not recommended as first-line therapy because in one study initial treatment with an α-blocker resulted in worse cerebrovascular, heart failure, and combined cardiovascular outcomes than initial treatment with a diuretic (question 3, evidence statement 13).[29] There were no RCTs of good or fair quality comparing the following drug classes to the 4 recommended classes: dual α_1- + β-blocking agents (eg, carvedilol), vasodilating β-blockers (eg, nebivolol), central α_2-adrenergic agonists (eg, clonidine), direct vasodilators (eg, hydralazine), aldosterone receptor antagonists (eg, spironolactone), adrenergic neuronal depleting agents (reserpine), and loop diuretics (eg, furosemide) (question 3, evidence statement 30). Therefore, these drug classes are not recommended as first-line therapy. In addition, no eligible RCTs were identified that compared a diuretic vs an ARB, or an ACEI vs an ARB. ONTARGET was not eligible because hypertension was not required for inclusion in the study.[30]

Similar to those for the general population, this recommendation applies to those with diabetes because trials including participants with diabetes showed no differences in major cardiovascular or cerebrovascular outcomes from those in the general population (question 3, evidence statements 36-48).

Table 4. Evidence-Based Dosing for Antihypertensive Drugs

Antihypertensive Medication	Initial Daily Dose, mg	Target Dose in RCTs Reviewed, mg	No. of Doses per Day
ACE inhibitors			
Captopril	50	150-200	2
Enalapril	5	20	1-2
Lisinopril	10	40	1
Angiotensin receptor blockers			
Eprosartan	400	600-800	1-2
Candesartan	4	12-32	1
Losartan	50	100	1-2
Valsartan	40-80	160-320	1
Irbesartan	75	300	1
β-Blockers			
Atenolol	25-50	100	1
Metoprolol	50	100-200	1-2
Calcium channel blockers			
Amlodipine	2.5	10	1
Diltiazem extended release	120-180	360	1
Nitrendipine	10	20	1-2
Thiazide-type diuretics			
Bendroflumethiazide	5	10	1
Chlorthalidone	12.5	12.5-25	1
Hydrochlorothiazide	12.5-25	25-100[a]	1-2
Indapamide	1.25	1.25-2.5	1

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.

[a]Current recommended evidence-based dose that balances efficacy and safety is 25-50 mg daily.

The following important points should be noted. First, many people will require treatment with more than one antihypertensive drug to achieve BP control. While this recommendation applies only to the choice of the initial antihypertensive drug, the panel suggests that any of these 4 classes would be good choices as add-on agents (recommendation 9). Second, this recommendation is specific for thiazide-type diuretics, which include thiazide diuretics, chlorthalidone, and indapamide; it does not include loop or potassium-sparing diuretics. Third, it is important that medications be dosed adequately to achieve results similar to those seen in the RCTs (Table 4). Fourth, RCTs that were limited to specific nonhypertensive populations, such as those with coronary artery disease or heart failure, were not reviewed for this recommendation. Therefore, recommendation 6 should be applied with caution to these populations. Recommendations for those with CKD are addressed in recommendation 8.

Recommendation 7

In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.

For general black population: Moderate Recommendation – Grade B
For black patients with diabetes: Weak Recommendation – Grade C

Recommendation 7 is based on evidence statements from question 3. In cases for which evidence for the black population was the same as for the general population, the evidence statements for the general population apply to the black population. However, there are some cases for which the results for black persons were different from the results for the general population (question 3, evidence statements 2, 10, and 17). In those cases, separate evidence statements were developed.

This recommendation stems from a prespecified subgroup analysis of data from a single large trial (ALLHAT) that was rated good.[31] In that study, a thiazide-type diuretic was shown to be more effective in improving cerebrovascular, heart failure, and combined cardiovascular outcomes compared to an ACEI in the black patient subgroup, which included large numbers of diabetic and nondiabetic participants (question 3, evidence statements 10, 15 and 17). Therefore, the recommendation is to choose thiazide-type diuretics over ACEI for black patients. Although a CCB was less effective than a diuretic in preventing heart failure in the black subgroup of this trial (question 3, evidence statement 14), there were no differences in other outcomes (cerebrovascular, CHD, combined cardiovascular, and kidney outcomes, or overall mortality) between a CCB and a diuretic (question 3, evidence statements 6, 8, 11, 18, and 19). Therefore, both thiazide-type diuretics and CCBs are recommended as first-line therapy for hypertension in black patients.

The panel recommended a CCB over an ACEI as first-line therapy in black patients because there was a 51% higher rate (relative risk, 1.51; 95% CI, 1.22-1.86) of stroke in black persons in ALLHAT with the use of an ACEI as initial therapy compared with use of a CCB (question 3, evidence statement 2).[32] The ACEI was also less effective in reducing BP in black individuals compared with the CCB (question 3, evidence statement 2).[32] There were no outcome studies meeting our eligibility criteria that compared diuretics or CCBs vs β-blockers, ARBs, or other renin-angiotensin system inhibitors in black patients.

The recommendation for black patients with diabetes is weaker than the recommendation for the general black population because outcomes for the comparison between initial use of a CCB compared to initial use of an ACEI in black persons with diabetes were not reported in any of the studies eligible for our evidence review.

Therefore, this evidence was extrapolated from findings in the black participants in ALLHAT, 46% of whom had diabetes. Additional support comes from a post hoc analysis of black participants in ALLHAT that met the criteria for the metabolic syndrome, 68% of whom had diabetes.[33] However, this study did not meet the criteria for our review because it was a post hoc analysis. This recommendation also does not address black persons with CKD, who are addressed in recommendation 8.

Recommendation 8

In the population aged 18 years or older with CKD and hypertension, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status.
Moderate Recommendation – Grade B

The evidence is moderate (question 3, evidence statements 31-32) that treatment with an ACEI or ARB improves kidney outcomes for patients with CKD. This recommendation applies to CKD patients with and without proteinuria, as studies using ACEIs or ARBs showed evidence of improved kidney outcomes in both groups.

This recommendation is based primarily on kidney outcomes because there is less evidence favoring ACEI or ARB for cardiovascular outcomes in patients with CKD. Neither ACEIs nor ARBs improved cardiovascular outcomes for CKD patients compared with a β-blocker or CCB (question 3, evidence statements 33-34). One trial (IDNT) did show improvement in heart failure outcomes with an ARB compared with a CCB, but this trial was restricted to a population with diabetic nephropathy and proteinuria (question 3, evidence statement 5).[34] There are no RCTs in the evidence review that directly compared ACEI to ARB for any cardiovascular outcome. However, both are renin-angiotensin system inhibitors and have been shown to have similar effects on kidney outcomes (question 3, evidence statements 31-32).

Recommendation 8 is specifically directed at those with CKD and hypertension and addresses the potential benefit of specific drugs on kidney outcomes. The AASK study showed the benefit of an ACEI on kidney outcomes in black patients with CKD and provides additional evidence that supports ACEI use in that population.[21] Additional trials that support the benefits of ACEI or ARB therapy did not meet our inclusion criteria because they were not restricted to patients with hypertension.[35,36] Direct renin inhibitors are not included in this recommendation because there were no studies demonstrating their benefits on kidney or cardiovascular outcomes.

The panel noted the potential conflict between this recommendation to use an ACEI or ARB in those with CKD and hypertension and the recommendation to use a diuretic or CCB (recommendation 7) in black persons: what if the person is black and has CKD? To answer this, the panel relied on expert opinion. In black patients with CKD and proteinuria, an ACEI or ARB is recommended as initial therapy because of the higher likelihood of progression to ESRD.[21] In black patients with CKD but without proteinuria, the choice for initial therapy is less clear and includes a thiazide-type diuretic, CCB, ACEI, or ARB. If an ACEI or ARB is not used as the initial drug, then an ACEI or ARB can be added as a second-line drug if necessary to achieve goal BP. Because the majority of patients with CKD and hypertension will require more than 1 drug to achieve goal BP, it is anticipated that an ACEI or ARB will be used either as initial therapy or as second-line therapy in addition to a diuretic or CCB in black patients with CKD.

Recommendation 8 applies to adults aged 18 years or older with CKD, but there is no evidence to support renin-angiotensin system inhibitor treatment in those older than 75 years. Although treatment with an ACEI or ARB may be beneficial in those older than 75 years, use of a thiazide-type diuretic or CCB is also an option for individuals with CKD in this age group.

Use of an ACEI or an ARB will commonly increase serum creatinine and may produce other metabolic effects such as hyperkalemia, particularly in patients with decreased kidney function. Although an increase in creatinine or potassium level does not always require adjusting medication, use of renin-angiotensin system inhibitors in the CKD population requires monitoring of electrolyte and serum creatinine levels, and in some cases, may require reduction in dose or discontinuation for safety reasons.

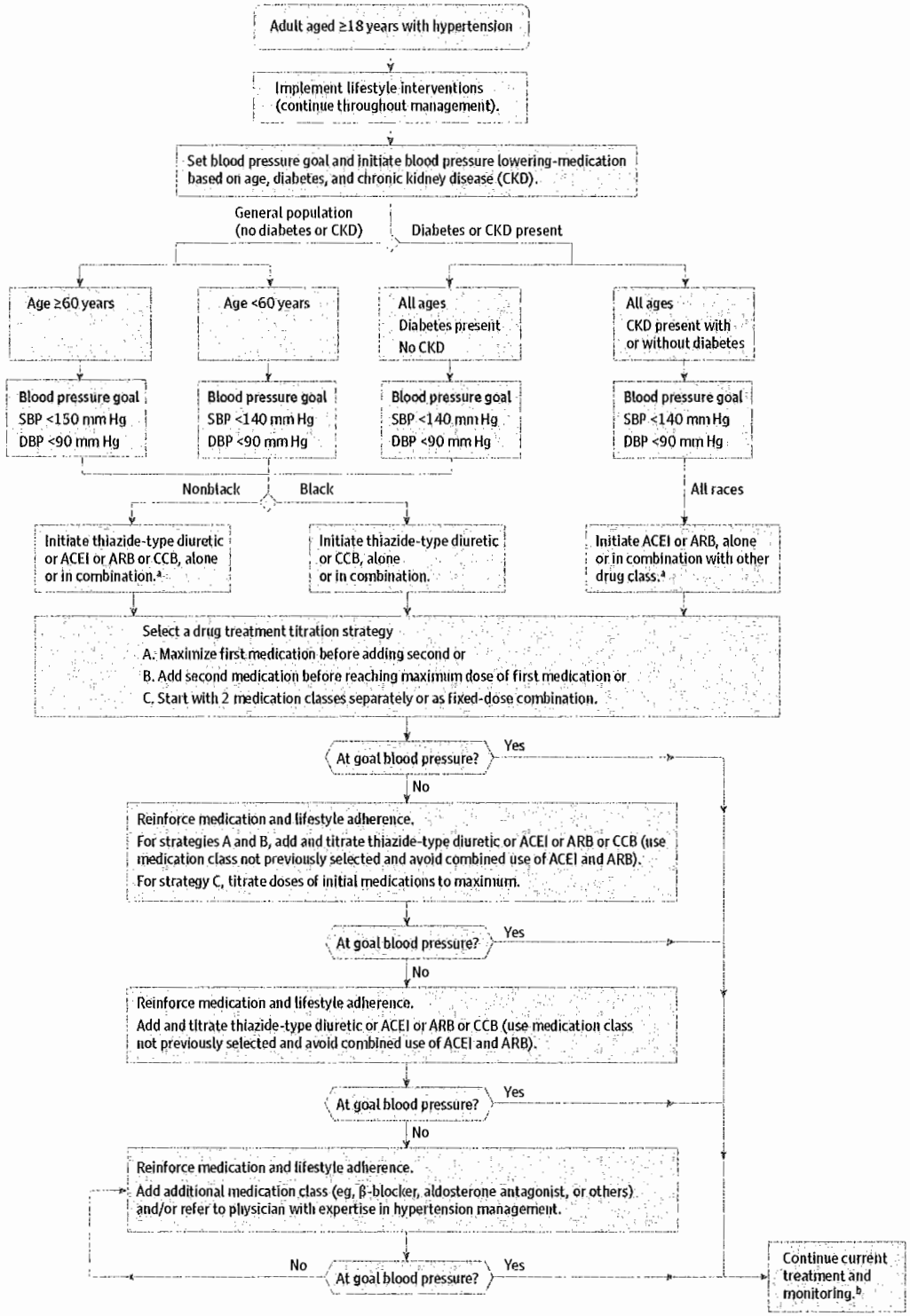
Recommendation 9

The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed.
Expert Opinion – Grade E

Recommendation 9 was developed by the panel in response to a perceived need for further guidance to assist in implementation of recommendations 1 through 8. Recommendation 9 is based on strategies used in RCTs that demonstrated improved patient outcomes and the expertise and clinical experience of panel members. This recommendation differs from the other recommendations because it was not developed in response to the 3 critical questions using a systematic review of the literature. The **Figure** is an algorithm summarizing the recommendations. However, this algorithm has not been validated with respect to achieving improved patient outcomes.

How should clinicians titrate and combine the drugs recommended in this report? There were no RCTs and thus the panel relied on expert opinion. Three strategies (**Table 5**) have been used in RCTs of high BP treatment but were not compared with each other. Based on the evidence reviewed for questions 1 through 3 and on the expert opinion of the panel members, it is not known if one of the strategies results in improved cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality compared with an alternative strategy. There is not likely to be evidence from well-designed RCTs that compare these

Figure. 2014 Hypertension Guideline Management Algorithm



SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.

[a] ACEIs and ARBs should not be used in combination.

[b] If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.

Table 5. Strategies to Dose Antihypertensive Drugs[a]

Strategy	Description	Details
A	Start one drug, titrate to maximum dose, and then add a second drug	If goal BP is not achieved with the initial drug, titrate the dose of the initial drug up to the maximum recommended dose to achieve goal BP If goal BP is not achieved with the use of one drug despite titration to the maximum recommended dose, add a second drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB) and titrate up to the maximum recommended dose of the second drug to achieve goal BP If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose to achieve goal BP
B	Start one drug and then add a second drug before achieving maximum dose of the initial drug	Start with one drug then add a second drug before achieving the maximum recommended dose of the initial drug, then titrate both drugs up to the maximum recommended doses of both to achieve goal BP If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose to achieve goal BP
C	Begin with 2 drugs at the same time, either as 2 separate pills or as a single pill combination	Initiate therapy with 2 drugs simultaneously, either as 2 separate drugs or as a single pill combination. Some committee members recommend starting therapy with ≥2 drugs when SBP is >160 mm Hg and/or DBP is >100 mm Hg, or if SBP is >20 mm Hg above goal and/or DBP is >10 mm Hg above goal. If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose.

Abbreviations: ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]This table is not meant to exclude other agents within the classes of antihypertensive medications that have been recommended but reflects those agents and dosing used in randomized controlled trials that demonstrated improved outcomes.

strategies and assess their effects on important health outcomes. There may be evidence that different strategies result in more rapid attainment of BP goal or in improved adherence, but those are intermediate outcomes that were not included in the evidence review. Therefore, each strategy is an acceptable pharmacologic treatment strategy that can be tailored based on individual circumstances, clinician and patient preferences, and drug tolerability. With each strategy, clinicians should regularly assess BP, encourage evidence-based lifestyle and adherence interventions, and adjust treatment until goal BP is attained and maintained. In most cases, adjusting treatment means intensifying therapy by increasing the drug dose or by adding additional drugs to the regimen. To avoid unnecessary complexity in this report, the hypertension management algorithm (Figure) does not explicitly define all potential drug treatment strategies.

Finally, panel members point out that in specific situations, one antihypertensive drug may be replaced with another if it is perceived not to be effective or if there are adverse effects.

Limitations

This evidence-based guideline for the management of high BP in adults is not a comprehensive guideline and is limited in scope because of the focused evidence review to address the 3 specific questions (Table 1). Clinicians often provide care for patients with numerous comorbidities or other important issues related to hypertension, but the decision was made to focus on 3 questions considered to be relevant to most physicians and patients. Treatment adherence and medication costs were thought to be beyond the scope of this review, but the panel acknowledges the importance of both issues.

The evidence review did not include observational studies, systematic reviews, or meta-analyses, and the panel did not conduct its own meta-analysis based on prespecified inclusion criteria. Thus, information from these types of studies was not incorporated into the evidence statements or recommendations. Although this may be considered a limitation, the panel decided to focus only on RCTs because they represent the best scientific evidence and because there were a substantial number of studies that included large numbers of patients and met our inclusion criteria. Randomized controlled trials that included participants with normal BP were excluded from our formal analysis. In cases in which high-quality evidence was not available or the evidence was weak or absent, the panel relied on fair-quality evidence, panel members' knowledge of the published literature beyond the RCTs reviewed, and personal experience to make recommendations. The duration of the guideline development process following completion of the systematic search may have caused the panel to miss studies published after our literature review. However, a bridge search was performed through August 2013, and the panel found no additional studies that would have changed the recommendations.

Many of the reviewed studies were conducted when the overall risk of cardiovascular morbidity and mortality was substantially higher than it is today; therefore, effect sizes may have been overestimated. Further, RCTs that enrolled prehypertensive or nonhypertensive individuals were excluded. Thus, our recommendations do not apply to those without hypertension. In many studies focused on DBP, participants also had elevated SBP so it was not possible to determine whether the benefit observed in those trials arose from lowering DBP, SBP, or both. In addition, the ability to compare studies from different time periods was limited by differences in clinical trial design and analytic techniques.

While physicians use cost, adherence, and often observational data to make treatment decisions, medical interventions should whenever possible be based first and foremost on good science demonstrating benefits to patients. Randomized controlled trials are the gold standard for this assessment and thus were the basis for providing the evidence for our clinical recommendations. Although adverse effects and harms of antihypertensive treatment documented in the RCTs were considered when the panel made its decisions, the review was not designed to determine whether therapy-associated adverse effects and harms resulted in significant changes in important health outcomes. In addition, this guide-

Table 6. Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; black: thiazide-type diuretic or CCB
	General <60 y	<140/90	
	Diabetes	<140/90	Thiazide-type diuretic, ACEI, ARB, or CCB
	CKD	<140/90	ACEI or ARB
ESH/ESC 2013[37]	General nonelderly	<140/90	Diuretic, β-blocker, CCB, ACEI, or ARB
	General elderly <80 y	<150/90	
	General ≥80 y	<150/90	
	Diabetes	<140/85	ACEI or ARB
	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	
CHEP 2013[38]	General <80 y	<140/90	Thiazide, β-blocker (age <60y), ACEI (nonblack), or ARB
	General ≥80 y	<150/90	
	Diabetes	<130/80	ACEI or ARB with additional CVD risk ACEI, ARB, thiazide, or DHPCCB without additional CVD risk
	CKD	<140/90	ACEI or ARB
ADA 2013[39]	Diabetes	<140/80	ACEI or ARB
KDIGO 2012[40]	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	
NICE 2011[41]	General <80 y	<140/90	<55 y: ACEI or ARB
	General ≥80 y	<150/90	≥55 y or black: CCB
ISHIB 2010[42]	Black, lower risk	<135/85	Diuretic or CCB
	Target organ damage or CVD risk	<130/80	

Abbreviations: ADA, American Diabetes Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; DHPCCB, dihydropyridine calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISHIB, International Society for Hypertension in Blacks; JNC, Joint National Committee; KDIGO, Kidney Disease: Improving Global Outcome; NICE, National Institute for Health and Clinical Excellence.

line was not endorsed by any federal agency or professional society prior to publication and thus is a departure from previous JNC reports. The panel anticipates that an objective assessment of this report following publication will allow open dialogue among endorsing entities and encourage continued attention to rigorous methods in guideline development, thus raising the standard for future guidelines.

Discussion

The recommendations based on RCT evidence in this guideline differ from recommendations in other currently used guidelines supported by expert consensus (**Table 6**). For example, JNC 7 and other guidelines recommended treatment to lower BP goals in patients with diabetes and CKD based on observational studies.[12] Recently, several guideline documents such as those from the American Diabetes Association have raised the systolic BP goals to values that are similar to those recommended in this evidence-based guideline.[37-42] Other guidelines such as those of the European Society of Hypertension/European Society of Cardiology also recommend a systolic BP goal of lower than 150 mm Hg, but it is not clear at what age cutoff in the general population this goal specifically applies.[37] This changing landscape is understandable given the lack of clear RCT evidence in many clinical situations.

History of JNC 8

The panel was originally constituted as the "Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8)." In March 2008 NHLBI sent letters inviting the co-chairs and committee members to serve on JNC 8. The charge to the committee was as follows: "The JNC 8 will review and synthesize the latest available scientific evidence, update existing clinical recommendations, and provide guidance to busy primary care clinicians on the best approaches to manage and control hypertension in order to minimize patients' risk for cardiovascular and other complications." The committee was also asked to identify and prioritize the most important questions for the evidence review. In June 2013, NHLBI announced its decision to discontinue developing clinical guidelines including those in process, instead partnering with selected organizations that would develop the guidelines.[43,44] Importantly, participation in this process required that these organizations be involved in producing the final content of the report. The panel elected to pursue publication independently to bring the recommendations to the public in a timely manner while maintaining the integrity of the predefined process. This report is therefore not an NHLBI sanctioned report and does not reflect the views of NHLBI.

Conclusions

It is important to note that this evidence-based guideline has not redefined high BP, and the panel believes that the 140/90 mm Hg definition from JNC 7 remains reasonable. The relationship between naturally occurring BP and risk is linear down to very low BP, but the benefit of treating to these lower levels with antihypertensive drugs is not established. For all persons with hypertension, the potential benefits of a healthy diet, weight control, and regular exercise cannot be overemphasized. These lifestyle treatments have the potential to improve BP control and even reduce medication needs. Al-

though the authors of this hypertension guideline did not conduct an evidence review of lifestyle treatments in patients taking and not taking antihypertensive medication, we support the recommendations of the 2013 Lifestyle Work Group.[45]

The recommendations from this evidence-based guideline from panel members appointed to the Eighth Joint National Committee (JNC 8) offer clinicians an analysis of what is known and not known about BP treatment thresholds, goals, and drug treatment strategies to achieve those goals based on evidence from RCTs. However, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient. We hope that the algorithm will facilitate implementation and be useful to busy clinicians. The strong evidence base of this report should inform quality measures for the treatment of patients with hypertension.

ARTICLE INFORMATION

Published Online: December 18, 2013. doi:10.1001/jama.2013.284427.

Author Affiliations: University of Iowa, Iowa City (James, Carter); University of Alabama at Birmingham School of Medicine (Oparil); Memphis Veterans Affairs Medical Center and the University of Tennessee, Memphis (Cushman); Johns Hopkins University School of Nursing, Baltimore, Maryland (Dennison-Himmelfarb); Kaiser Permanente, Anaheim, California (Handler); Medical University of South Carolina, Charleston (Lackland); University of Missouri, Columbia (LeFevre); Denver Health and Hospital Authority and the University of Colorado School of Medicine, Denver (MacKenzie); New York University School of Medicine, New York, New York (Ogedegbe); University of North Carolina at Chapel Hill (Smith); Duke University, Durham, North Carolina (Svetkey); Mayo Clinic College of Medicine, Rochester, Minnesota (Taler); University of Pennsylvania, Philadelphia (Townsend); Case Western Reserve University, Cleveland, Ohio (Wright); National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland (Narva); at the time of the project, National Heart, Lung, and Blood Institute, Bethesda, Maryland (Ortiz); currently with ProVation Medical, Wolters Kluwer Health, Minneapolis, Minnesota (Ortiz).

Author Contributions: Drs James and Oparil had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept ond design, ocquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical, and material support, and *study supervision:* All authors.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Oparil reports individual and institutional payment related to board membership from Bayer, Daiichi Sankyo, Novartis, Medtronic, and Takeda; individual consulting fees from Backbeat, Bayer, Boehringer-Ingelheim, Bristol Myers-Squibb, Daiichi Sankyo, Eli Lilly, Medtronic, Merck, Pfizer, and Takeda; receipt of institutional grant funding from AstraZeneca, Daiichi Sankyo, Eisai Inc, Gilead, Medtronic, Merck, Novartis, Takeda Global Research and Development Inc; individual payment for lectures from Daiichi Sankyo, Merck, Novartis, and Pfizer; individual and institutional payment for development of educational presentations from ASH/AHSR (Daiichi Sankyo); and individual and institutional payment from Amarin Pharma Inc, Daiichi Sankyo, and LipoScience Inc for educational grant(s) for the Annual UAB Vascular Biology & Hypertension Symposium. Dr Cushman reports receipt of institutional grant support from Merck, Lilly, and Novartis; and consulting fees from Novartis, Sciele Pharmaceuticals, Takeda, sanofi-aventis, Gilead, Calpis, Pharmacopeia, Theravance, Daiichi-Sankyo, Noven, AstraZeneca Spain, Merck, Omron, and Janssen. Dr Townsend reports board membership with Medtronic, consultancy for Janssen, GlaxoSmithKline, and Merck, and royalties/educational-related payments from Merck, UpToDate, and Medscape. Dr Wright reports receipt of consulting fees from Medtronic, CVRx, Takeda, Daiichi-Sankyo, Pfizer, Novartis, and Take Care Health. The other authors report no disclosures.

Funding/Support: The evidence review for this project was funded by the National Heart, Lung, and Blood Institute (NHLBI).

Role of the Sponsor: The design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication are the responsibilities of the authors alone and independent of NHLBI.

Disclaimer: The views expressed do not represent those of the NHLBI, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health, or the federal government.

Additional Contributions: We thank Cory V. Evans, MPP, who at the time of the project was a senior research analyst and contract lead for JNC 8 with Leidos (formerly Science Applications International Corporation) and Linda J. Lux, MPA, RTI International, for their support. We also thank Lawrence J. Fine, MD, DrPH, NHLBI, for his work with the panel. Those named here were compensated in their roles as consultants on the project.

Correction: This article was corrected for the description of reserpine in Recommendation 6, addition of a footnote to Table 5, and text in the Discussion on January 21, 2014.

REFERENCES

1. Staessen JA, Fagard R, Thijs L, et al; The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet*. 1997;350(9080):757-764.

2. Beckett NS, Peters R, Fletcher AE, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358(18):1887-1898.

3. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265(24):3255-3264.

4. Institute of Medicine. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011. http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx. Accessed November 4, 2013.

5. Hsu CC, Sandford BA. The Delphi technique: making sense of consensus. *Pract Assess Res Eval*. 2007;12(10). http://pareonline.net/pdf/v12n10.pdf. Accessed October 28, 2013.

6. Institute of Medicine. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: National Academies Press; 2011. http://www.iom.edu/Reports/2011/Finding-What-Works-in-Health-Care-Standards-for-systematic-Reviews.aspx. Accessed November 6, 2013.

7. Cushman WC, Evans GW, Byington RP, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575-1585.

8. Benavente OR, Coffey CS, Conwit R, et al; SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013;382(9891):507-515.

9. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res*. 2008;31(12):2115-2127.

10. Ogihara T, Saruta T, Rakugi H, et al; Valsartan in Elderly Isolated Systolic Hypertension Study Group. Target blood pressure for treatment of isolated systolic hypertension in the elderly: Valsartan in Elderly Isolated Systolic Hypertension Study. *Hypertension*. 2010;56(2):196-202.

11. Verdecchia P, Staessen JA, Angeli F, et al; Cardio-Sis investigators. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet*. 2009;374(9689):525-533.

12. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-2572.

13. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program, I: reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA*. 1979;242(23):2562-2571.

14. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program, III: reduction in stroke incidence among persons with high blood pressure. *JAMA*. 1982;247(5):633-638.

15. Hypertension-Stroke Cooperative Study Group. Effect of antihypertensive treatment on stroke recurrence. *JAMA*. 1974;229(4):409-418.

16. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J (Clin Res Ed)*. 1985;291(6488):97-104.

17. Report by the Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet*. 1980;1(8181):1261-1267.

18. Effects of treatment on morbidity in hypertension, II: results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA*. 1970;213(7):1143-1152.

19. Hansson L, Zanchetti A, Carruthers SG, et al; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998;351(9118):1755-1762.

20. Ruggenenti P, Perna A, Loriga G, et al; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*. 2005;365(9463):939-946.

21. Wright JT Jr, Bakris G, Greene T, et al; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288(19):2421-2431.

22. Klahr S, Levey AS, Beck GJ, et al; Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med*. 1994;330(13):877-884.

23. Curb JD, Pressel SL, Cutler JA, et al; Systolic Hypertension in the Elderly Program Cooperative Research Group. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA*. 1996;276(23):1886-1892.

24. Tuomilehto J, Rastenyte D, Birkenhäger WH, et al; Systolic Hypertension in Europe Trial Investigators. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med*. 1999;340(9):677-684.

25. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317(7160):703-713.

26. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370(9590):829-840.

27. The IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J Hypertens*. 1985;3(4):379-392.

28. Dahlöf B, Devereux RB, Kjeldsen SE, et al; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359(9311):995-1003.

29. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension*. 2003;42(3):239-246.

30. Yusuf S, Teo KK, Pogue J, et al; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559.

31. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial: major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA*. 2002;288(23):2981-2997.

32. Leenen FH, Nwachuku CE, Black HR, et al; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Hypertension*. 2006;48(3):374-384.

33. Wright JT Jr, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2008;168(2):207-217.

34. Lewis EJ, Hunsicker LG, Clarke WR, et al; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851-860.

35. Brenner BM, Cooper ME, de Zeeuw D, et al; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-869.

36. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329(20):1456-1462.

37. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159-2219.

38. Hypertension without compelling indications: 2013 CHEP recommendations. Hypertension Canada website. http://www.hypertension.ca/hypertension-without-compelling-indications. Accessed October 30, 2013.

39. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care*. 2013;36(suppl 1):S11-S66.

40. Kidney Disease; Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl*. 2012;2(5):337-414.

41. National Institute for Health and Clinical Excellence. Hypertension (CG127). http://www.nice.org.uk/guidance/cg127. Accessed October 30, 2013.

42. Flack JM, Sica DA, Bakris G, et al; International Society on Hypertension in Blacks. Management of high blood pressure in Blacks: an update of the International Society on Hypertension in Blacks consensus statement. *Hypertension*. 2010;56(5):780-800.

43. Gibbons GH, Harold JG, Jessup M, Robertson RM, Oetgen WJ. The next steps in developing clinical practice guidelines for prevention. *J Am Coll Cardiol*. 2013;62(15):1399-1400.

44. Gibbons GH, Shurin SB, Mensah GA, Lauer MS. Refocusing the agenda on cardiovascular guidelines: an announcement from the National Heart, Lung, and Blood Institute. *Circulation*. 2013;128(15):1713-1715.

45. Eckel RH, Jakicic JM, Ard JD, et al. AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2013. doi:10.1161/01.cir.0000437740.48606.d1.